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ORIGINAL ARTICLES.

STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

III. THE PREFIBRILLATORY MECHANISM DURING ESTABLISHED AURICULO-VENTRICULAR DISSOCIATION.

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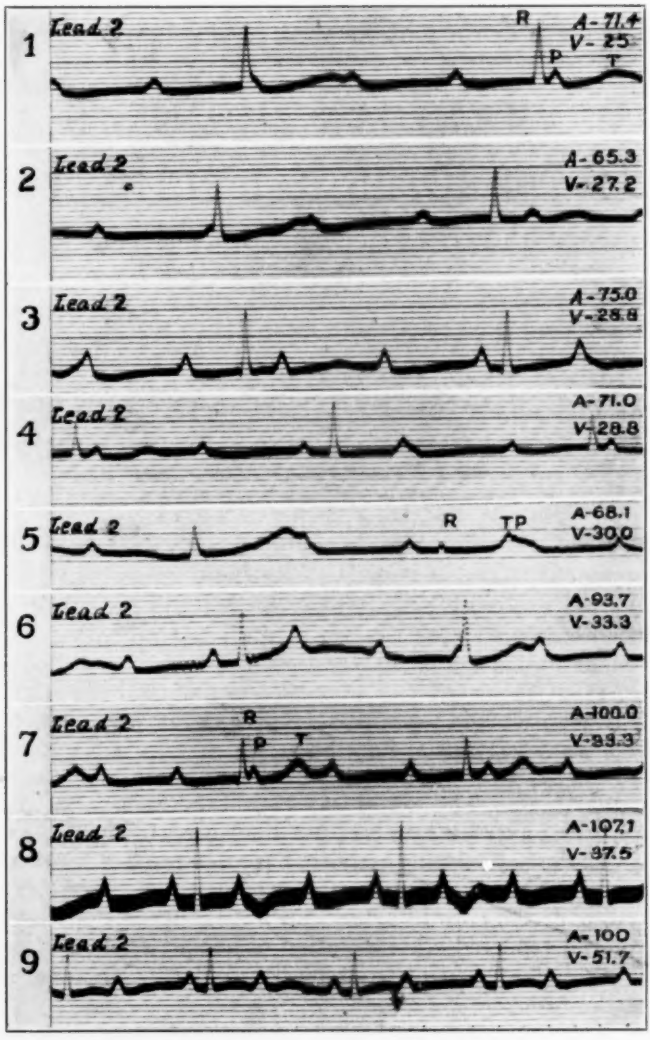
THE alterations in the rhythm of the heart preceding transient ventricular fibrillation in the presence of established *A-V* dissociation are often associated with an acceleration of the basic ventricular rate. In 6 patients in whom the ventricular rate was studied prior to the onset of ventricular fibrillation, the average basic ventricular rate was 25 beats per minute without the interposition of premature ventricular beats. The lowest was 17 and the highest 38 beats per minute. The average rate was not influenced by rest or exercise and it was the same during activity, but an average of 6 beats lower during sleep when counts were taken over long periods at a time. Pressure over the carotid artery did not influence the ventricular rhythm and repeated administration of adequate doses of atropin sulphate ($\frac{1}{50}$th grain) intramuscularly yielded no increase in the ventricular rate.

The Modes of Acceleration of the Basic Ventricular Rate During A-V Dissociation. The acceleration of the basic ventricular rate preceding ventricular fibrillation may be effected through several mechanisms. (A) There may be a simple and progressive shortening of the interventricular periods so that a ventricular rate of 25 beats per minute may rise to 51.7 beats within a short interval (Fig. A 1-9). At such times the impulse pacemaker of the ventricles is very likely within the *A-V* node, for the complexes of the main

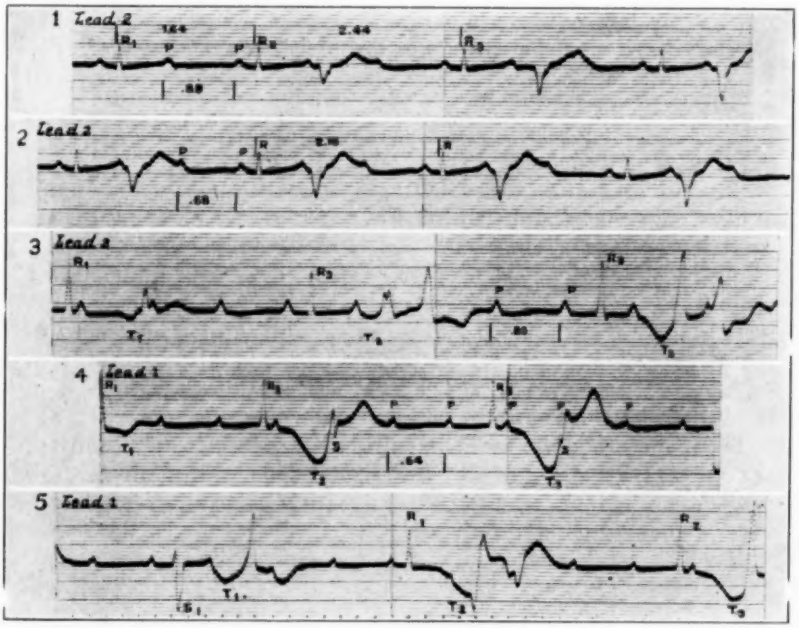
ventricular deflections are of the supraventricular type and vary but little from beat to beat.



A. Electrocardiograms (Lead 2 only) showing a progressive increase in the basic auricular and ventricular rates preceding a transient seizure of auricular fibrillation.

(B) On other occasions, a gradual acceleration of the ventricular rate from an average of 37 beats per minute to 65.2 beats, independent of premature beats may take place through a steplike progression of both auricles and ventricles with abrupt changes from com-

plete *A–V* dissociation to partial heart block.[1] Invariably with these abrupt changes there is an accompanying transition of the ventricular deflections from a dextrogram to a levogram and *vice versa* indicating that each successive new pacemaker is somewhere in one of the bundles of the conduction mechanism and alternates with a supraventricular mechanism. When the heart rate has thus been accelerated gradually to a certain level of speed, it is then suddenly interrupted by at first single and then recurrent groups of ventricular oscillations of wide aberrancy that herald the approach of a period of ventricular fibrillation.



B. Electrocardiograms (Lead 2 only) showing the prefibrillatory mechanism in a patient with transient ventricular fibrillation.

(C) Again a very marked increase in the basic ventricular rate is observed to appear abruptly after the ventricles had been already speeded up from an average of 20 to 70 beats per minute, when a greater rate would be ushered in by the interruption of a single extrasystole. This extrasystole was always of a different shape, size and form from both the preceding and succeeding ventricular complexes. It resembled the experimental stimulus with which it is frequently possible to step up the ventricles when isolated from the auricles by the interposition of a well timed beat.

(D) Occasionally a transient seizure of ventricular fibrillation is ushered in by the recurrence of short runs of tachycardia arising

in an ectopic focus of the ventricles, when periods of *A–V* dissociation and ventricular tachycardias alternate haphazardly for a variable duration until the whole cardiac mechanism is disrupted by the interposition of ventricular oscillations resembling short runs of ventricular fibrillation and then the patient goes into syncope.

(E) Rarely the periods of complete heart block was suddenly disrupted by an irregular heart rate of an average of 160 beats per minute, during which the auricles kept pace with the ventricles as far as rate was concerned but both chambers beat independently of each other. This mechanism was one of an irregular ventricular tachycardia ushering in a period of ventricular fibrillation. It is very likely that many terminal tachycardias preceding ventricular fibrillation arise in a similar manner without any warning, especially if some form of block has been present before or has been induced by a drug.

(F) More often a low basic ventricular rate (from 20 to 30 beats per minute) was increased by the appearance of premature beats of the ventricles, at first coming singly (Fig. C-1) and then in groups of more than one (Fig. C-2, 3, 4, 5, 6). These were observed during partial as well as complete heart block.

The main ventricular deflections of the electrocardiograms during established *A–V* dissociation were usually of the supraventricular form and were variable in height, shape and form from record to record (Fig. A-5, 6, 7) and in the same record they changed from dextrograms to levograms even in the absence of any increase in the ventricular rate (Fig. B-5).

The *T* waves of the basic ventricular complexes were usually of the upright form (Fig. A-5, 7) and were preceded by an *R–T* or *S–T* interval which was variable in duration, this variation depending apparently upon the rate of the ventricles, that is, the slower ventricular rates showed ventricular complexes with an *R–T* or *S–T* interval of longer duration (Compare the *R–T* interval in 5 and 7 of Fig. A). Both the shape and contour of the *S–T* interval as well as that of the *T* waves were invariably influenced by a superimposed auricular contraction. The size, shape and form of the *T* waves during these intervals were independent of the preceding *Q R S* complexes. The direction of the *T* waves remained the same even though the *Q R S* complexes reversed from dextrograms to levograms.

Deformed Ventricular Complexes in the Electrocardiograms of the Premonitory Period. The most marked changes of both the *Q R S* complexes as well as of the *T* waves of the dominant rhythm were observed occasionally during the premonitory period when the block was complete and when the basic rhythm was disrupted by premature ventricular beats which, judging from their shapes, "appeared" to arise from more than one focus (Figs. B-3, 4, 5, and C-4, 5, 6). At such times the main ventricular deflections were

C. Electrocardiograms (Lead 2 only). The prefibrillatory mechanism in a patient with transient periods of ventricular fibrillation during *A-V* dissociation. Note the regularity of the auricular wave during the short runs of fibrillation.

extremely variable in height, form and direction from beat to beat. The accompanying *S–T* interval of these deflections was usually shortened and the succeeding *T* waves of the electrocardiograms were occasionally found to have become progressively larger in size from beat to beat, variably deformed and markedly negative.

The deformities of the *T* waves were apparently related to the time of the appearance of the premature ventricular beats following the basic ventricular deflections. The earlier the *S–T* interval of the main ventricular deflection was interrupted by a premature beat of the ventricles, the greater appeared the size and negativity of the *T* waves. For example, in Figure B-4, R_1 is followed by a negative T_1 which is 2 mm. in depth; R_2 is followed by a markedly negative T_2 which is 9 mm. in depth and the same size in width and the next premature ventricular beat is continuous with its ascending limb; R_3 is followed by a negative T_3 which is 11 mm. in depth and from its ascending limb there arises practically one-half of a superimposed premature ventricular beat to be followed also by a markedly positive and large *T* wave (compare also Fig. C-4, 5, 6 and Fig. D, Lead 3).

Frequently the *S–T* interval of a basic ventricular deflection was disrupted by portions of two successive premature beats of the ventricles (Fig. B-5) one so superimposed upon the other as to give a most bizarre picture.

The auricular contractions were not interfered with during the appearance of these superimposed ventricular beats (Fig. C-4, 5, 6).

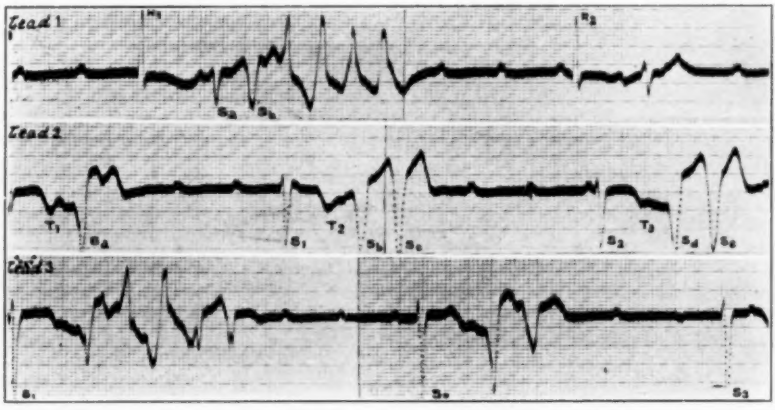
Sometimes, when the alternate premature ventricular beats following the basic ventricular complexes were of the same shape and form from beat to beat and seemed to arise from the same focus in the ventricles repeatedly (Fig. E, Leads 2 and 3) then the deformity of the *T* waves accompanying the main ventricular deflections was uniform and the *S–T* interval preceding it was of the same duration.

The shape, form and direction of the "initial" alternate premature ventricular beats (Fig. C-1, 2) which were the first to disrupt the basic heart rhythm, were at times extremely variable but more frequently, in particular before the development of long syncopal seizures, these beats were almost alike for minutes and hours at a time giving the impression that they arose from the same focus in the ventricles (Fig. E, Leads 2 and 3). They were usually opposite in direction to the main ventricular deflection and were uniformly distanced from the foot points of the antecedent ventricular complexes before the onset of a syncopal attack (Fig. F).

In hundreds of records obtained of the periods preceding transient ventricular fibrillation in these patients with *A–V* dissociation, not a single instance was encountered in which the onset of syncope was not heralded by premature ventricular beats coming either single, at alternate intervals, or in groups.

The shape of the ventricular oscillations that followed the "initial" premature ventricular beats varied. Sometimes they were opposite in direction to it but most often in the same direction (Fig. C-4).

The frequency and duration of the ventricular oscillations that followed the "initial" premature ventricular beat at any one time was unpredictable. In view of the fact that only the first few of the ventricular oscillations following the "initial" premature ventricular beat could be felt at the pulse, it is very obvious that the greater the duration and frequency of these succeeding ventricular complexes, which were associated with ineffectual contractions of the ventricles, the longer was the accompanying period of syncope.



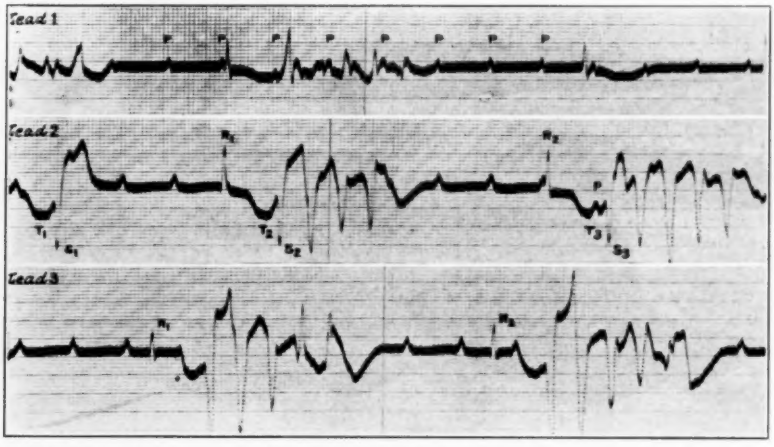
D. Electrocardiograms (Leads 1, 2, 3) of the prefibrillatory mechanism in a patient with *A–V* dissociation. Compare the basic ventricular complexes and the initial premature beat of this record with that of E.

The duration of the interventricular periods formed by the dominant ventricular complexes during the interruption of the rhythm by these premature ventricular beats was variable from minute to minute. These premature contractions were never observed to have been interpolated. The ventricular cycles succeeding the premature beats were variable, sometimes being equal and sometimes longer than the preceding periods.

Although during this premonitory period none of the recurrent groups of ventricular oscillations could be palpated at the wrist, save for the first few, some could be heard at the apex of the heart while others were neither audible at the apex nor palpable at the wrist. The electrocardiograms of these "audible" groups of beats were more regular in sequence than the latter. The ventricular complexes at such times were sharper and peaked, and although a uniform base line was absent, they remained of about the same size and duration in most of the records obtained, although occasionally their voltage was reduced (Fig. C-5, 6). In these "atypical" ventricular tachy-

cardias the *P* waves were more readily visible on the upstroke of every second beat (Fig. C-3, 4, 6) and what is of particular interest is that frequently these short runs were ended by groups of premature ventricular beats that were distinctly separated from each other by a baseline of short duration, none of which, however, could be palpated at the wrist. Such premature ventricular beats would end the period of tachycardia or would be followed by a postundulatory pause.

The ventricular rates during these tachycardias averaged 200 beats per minute and no such similar cardiac mechanism was recorded for a period longer than 3 seconds.

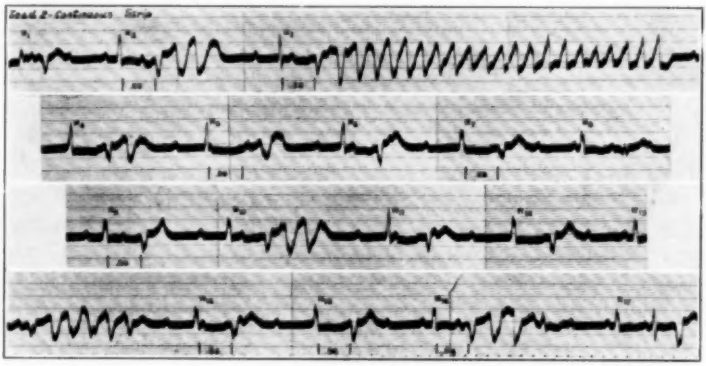


E. Electrocardiograms (Leads 1, 2, 3) showing the prefibrillatory mechanism in a patient with *A–V* dissociation. Compare this record with record D.

The Behavior of the Heart Rhythm Preceding Syncope Due to Standstill of the Ventricles. It is apparent from these records that the alterations in the rate and rhythm of the heart preceding syncopal seizures in patients with *A–V* dissociation and transient ventricular fibrillation are totally different from those patients in whom syncopal seizures are due to a slowing of the ventricular rate or complete standstill of the ventricles. In the latter group observations recorded to date reveal that the periods preceding syncopal seizures may be appreciated clinically, at times, by the periodic omission of a complete ventricular cycle. This may be followed by the absence of several alternate ventricular cycles, each one of these causing a pause which may be associated clinically with spots before the eyes or short periods of dizziness. More often, the ventricular cycles omitted may be two and three times the duration of normal cycles, especially when there are marked variations in the rate and rhythm of the idioventricular pacemaker so as to cause an inequality of the basic interventricular periods.

Again there may be a progressive increase in the interventricular periods from beat to beat until standstill of the ventricles finally takes place, these progressively lengthening heart pauses resembling very closely Luciani or Wenckenbach periods encountered so frequently in patients with partial heart block.[2]

Moreover, frequently, the transitional changes from partial to complete heart block resulting in syncope may be associated with a "preautomatic pause,"[3] and may be accompanied by a variable standstill of the whole heart at times involving absence of both auricular and ventricular contractions but more often ventricular contractions only.



F. Electrocardiograms (Lead 2 only) showing the initial premature beat to be at the same distance from the basic ventricular complex.

In each of the preceding mechanism in syncope, it is *slowing* of the ventricular rate that precedes the onset of unconsciousness.

The Influence of the Extrinsic Nervous Mechanism on the Auricles and Ventricles During Heart Block. There is some experimental evidence[4] substantiated by clinically correlated observations[5] that in certain instances syncope brought on by slowing of the ventricles, with certain exceptions[6] may be due to an increase in the auricular rate, in contradistinction to the syncope in patients with ventricular fibrillation in whom the auricular rate usually remains the same before the seizures. There can be no doubt that in some of these patients this acceleration of the auricular rate is in some way related to reflex stimulation of the extrinsic nervous mechanism of the heart.[7] These facts are emphasized at the present time because very recently Shookoff[8] reported a patient in whom during the presence of auricular fibrillation, pressure over the right common carotid artery (indirectly stimulating the vagus nerve to the heart) resulted in an irregularity considered to be that of ventricular fibrillation. The records published by him resemble more closely some of the large coarse irregular waves of impure flutter encoun-

tered either during so-called coarse auricular fibrillation or normal rhythm, several examples of which may be found in Geraudel's studies[9] and considered by him as "false ventricular fibrillation."

Ventricular fibrillation once established, even for brief periods, is practically never interrupted by a supraventricular complex before the fibrillatory process ends spontaneously and then only when a postundulatory pause does not precede restoration of the basic rhythm, does a premature beat or a markedly aberrant ventricular complex resembling it, end a seizure. Furthermore, as we have pointed out previously, in the thousands of brief periods of ventricular fibrillation that we have recorded, none have been observed to appear without at least one "initial" premature ventricular beat preceding the ventricular period during which fibrillation sets in. For these reasons we believe that Shookoff's case, the only clinical instance published to date in which reflex stimulation of the vagus nerve is held responsible for initiating transient ventricular fibrillation, may be based on a misinterpretation of the electrocardiograms recorded.

Summary and Conclusions. The clinical and electrocardiographic manifestations in 6 patients with *A–V* dissociation who exhibited recurrent syncopal attacks due to transient ventricular fibrillation have been correlated.

In each instance it was determined that the alterations in the rhythm of the heart preceding a period of ventricular fibrillation were characterized by an acceleration of the basic ventricular rate of the ventricles.

The acceleration of the ventricular rate preceding ventricular fibrillation in patients with *A–V* dissociation was effected through: A, A simple and progressive shortening of the interventricular periods; B, A steplike progression of both auricles and ventricules with abrupt changes from partial to complete heart block and *vice versa*, each alteration resulting in a further acceleration of the ventricular rate; C, the interposition of a single extrasystole changing a slower rhythm to a faster one with a concomitant change in the pacemaker of the ventricles; D, recurrent short runs of tachycardia arising in an ectopic focus of the ventricles and alternating with the periods of heart block; E, a tachysystole in which a rapid auricular rate kept pace with a rapid ventricular rate before fibrillation disrupted the whole cardiac mechanism and finally F, isolated premature beats of the ventricles which appeared in rapid succession and accelerated the heart before the cardiac mechanism responsible for syncope had set in.

On the basis of these correlated observations, it is fair to assume that a diagnosis of transient ventricular fibrillation may be suspected in a patient with *A–V* dissociation and syncopal attacks if any of these cardiac mechanisms are observed to appear either prior to or subsequent to syncopal seizures.

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BLOOD REGENERATION IN PATIENTS WITH HEMATEMESIS OR MELENA FROM PEPTIC ULCER, TREATED WITH THE USUAL ULCER CURE AND WITH THE MEULENGRACHT TREATMENT.

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In July, 1931, Meulengracht altered the treatment of patients with hematemesis or melena in this department. Previously, such patients were given the usual "ulcer cure." After a few days' fasting, they had cold tea or oatmeal gruel, advancing very slowly through milk and milk soups with sago, ricemeal, etc., to the "purée diet" which was generally attained after about 4 weeks. Meulengracht now gave this purée diet in its full extent from the first day of admission, which often meant from the first day of bleeding. This is a well-balanced diet which includes meat, fish, vegetables, fruit, potatoes, in fact all sorts of food, finely minced in the form of forcemeat, mashed potatoes, puréed vegetables, fruit soups, jellies, and so on. In addition, iron was given, and an aperient (*e. g.*, cascara). Meulengracht was induced to make this alteration chiefly from clinical observation and from the well-known experiments of Whipple, Hooper and Robscheit,[3] in which they showed that anemic dogs regenerate blood much better on certain diets, especially meat and liver, than when fasting or fed on carbohydrates and milk. There is no reason to suppose that human beings should react differently to hemorrhage.

The object of this communication is to show the difference in blood regeneration before and after Meulengracht's treatment was introduced.

Methods. The following hemoglobin estimations and red cell counts were made upon patients admitted for hematemesis or melena. In all patients, gastric or duodenal ulcer was supposed to be the source of the hemorrhage, patients with cancer of the stomach or cirrhosis of the liver being excluded, even though given the same treatment.

Blood was taken for examination about once a week. During the first week more examinations have been made in most patients.

Hemoglobin estimations were all made with the same Autenrieth-Königsberger hemometer. The same apparatus has been used daily since 1917; it has been standardized twice (in 1918 and 1934) with the oxygen capacity method (100% Hb = 18.5 cc. O_2). The correction has not altered measurably. Several times examination of series of normal persons has shown this standard to give a color index about 1. On each sample two readings were made and an average given. The red cell count was made in a Bürker-Türk chamber, 10 big squares being counted, making the cipher for multiplication 5000. All estimations of hemoglobin and counting of red cells were made on venous blood from the cubital vein, 3 to 4 cc. being stabilized by 3 drops of saturated solution of sodium oxalate. Correction for this surplus fluid has not been made. In all individual samples the hemoglobin estimation and the red cell count were made from the same blood by the same person, a technical assistant. About 95% of all determinations were made by one assistant, Miss Lundgreen, the rest were made by another technical assistant, Miss Norman-Hansen, but no difference could be detected between the values obtained by the two.

Patients on the Old Ulcer Cure. Most of these patients' records date from 1929 to 1931, a few from later years. They were all given the aforementioned ulcer cure, many were fasted for a few days; about 4 weeks after admission the purée diet was given, and most of the patients have had some iron medicament a little later.

Patients on Purée Diet and Iron. These patients all date from 1931 to 1935. The patients were given the purée diet from the first day of admission and also iron from the first day (ferrosi lactat., centigrams 50 × 3). The patients have not been pressed to eat but have followed their own appetite.

Results. As an example of how much this consumption of food could amount to, I give one day's experience, although, to be sure, this patient ate well above the average: A man, aged 37, from April 11, 1935, repeatedly had melena or hematemesis. On April 12, he was admitted to hospital and given the purée diet and iron, and on April 14 a transfusion of blood (300 cc.). On April 15, he had hematemesis for the last time. This day (before the hematemesis) his Hg % was 30 and his R.B.C. 1.42 millions. The next day, April 16, his consumption of food as controlled by the nurses was: In the morning: 150 gm. oatmeal porridge; for dinner (at 1 o'clock): fruit soup, boiled forcedmeat-balls and green-pea purée and in the evening; a soft-boiled egg and a little piece of white bread. Also, in the course of the day he drank 1 liter of milk and 1 glass of churned milk with cream and consumed 4 oranges, 2 bananas and

2 biscuits. The day after, April 17, his Hg % was 21 and the R.B.C. 0.87 million, but 19 days later, he had reached 67% and 3 millions.

One Patient Treated With Both Cures Successively. This patient was admitted 4 times, twice in 1928 and twice in 1932. The first time (January, 1928) she apparently had lost blood from her bowels without noticing it; she was sent in to be treated for anemia but had really regenerated her blood quite well on her usual diet. The second time she had melena and was treated with the ulcer cure (July to September, 1928). The third time (January, 1932) she had a hematemesis and was treated with the purée diet, but insufficient blood examinations were made to estimate her regeneration. The fourth time (September, 1932) she had melena and was given purée diet and iron. The curves of regeneration for the second and fourth admissions are shown on Fig. 1.

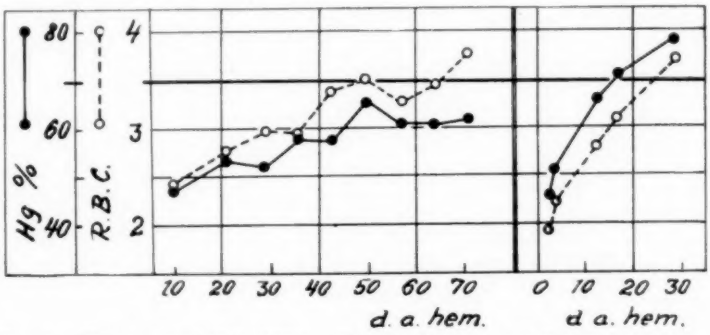

FIG. 1.—Woman, aged 48 (in 1928). To the left, Hg % and R.B.C. on ulcer cure. To the right, Hg % and R.B.C. on purée diet and iron. Ordinate: Hg % and R.B.C. Abscissæ: Days after hemorrhage.

Comparison Between the Two Groups. A comparison between the two groups can only be valid when the severity of the hemorrhage is taken into account. Even then, the individual's inherent ability to regenerate remains an unknown factor. For comparison, I have selected from each group those 10 patients whose red blood cell count on the first examination after admission was nearest to 2.5 millions. This examination was made on the first to the third day after admission. The patients were admitted on the first to the seventh day after the first bleeding. As far as possible such patients have been omitted where there is not at least 24 hours between the last known hemorrhage and the first blood examination. The average time from the first hemorrhage to admission is, for the ulcer cure group, 2.4 days and for the purée diet group 2.2 days and the average time from the first hemorrhage to the first blood examination is 4.4 and 3.9 days, respectively.

The two groups, besides, are comparable as to age and sex. No patient had known complications of any sort, or was given transfusion of blood or had hematemesis or apparently fresh melena after the first blood examination. Only a few, indeed, had more than one known hemorrhage.

TABLE 1.—AVERAGE BLOOD VALUES FOR PATIENTS ON ULCER CURE AND ON PURÉE DIET AND IRON.

	Hg % on adm.	R.B.C. on adm.	Hg % 20 days later.	R.B.C. 20 days later.
10 patients on ulcer cure .	47.5±2.1	2.43±0.10	50.0±1.9	2.80±0.09
10 patients on purée diet and iron	50.0±2.1	2.42±0.11	68.4±2.6	3.45±0.12
Difference	2.50±2.9	0.01±0.15	18.4±3.2	0.65±0.15

In the ulcer cure group, 4 patients had hematemesis, in the purée diet group 6; the other patients had only melena. The average Hg % estimations and R.B.C. counts in the two groups will be seen from Table 1, where the values from the first blood examination are compared to the values found 20 days later.

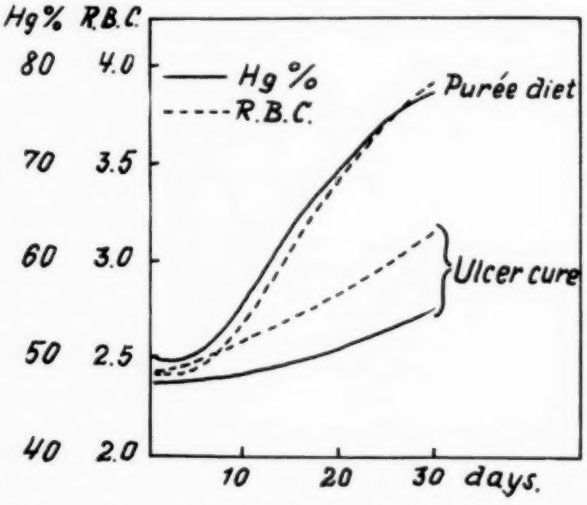

FIG. 2.—Balanced average curves of Hg % and R.B.C. count in patients on ulcer cure and purée diet. Upper curves: Patients on purée diet. Lower curves: Patients on ulcer cure. Ordinate: Hg % and R.B.C. Abscissæ: Days from first examination on admission.

Thus the difference between the two groups on admission is less than the medium error. The difference in the values for the two groups on the 20th day for Hg % is 18.4 ± 3.2; *i. e.*, 5.6 times the medium error and for the R.B.C. 0.65 ± 0.15; *i. e.*, 4.3 times the medium error. The highest Hg % on the 20th day in the ulcer-cure group is 57; only 1 in the other group is as low as

that. Fig. 2 presents balanced average curves of Hg % and R.B.C. in the two groups.

Hemoglobin and Blood Corpuscle Regeneration Compared. On the purée diet, the curves for hemoglobin and red blood cells follow each other very closely, the color index during the whole period being very near 1. In many patients, especially those who bled more severely than did the cases in this paper, it has even been well above 1. The patients on ulcer cure, on the other hand, regenerate the hemoglobin markedly slower than red corpuscles. Color index during the whole time of observation is low; on the 20th day, for example, 0.89 against 0.99 for the patients on purée diet.

The effect of iron cannot be estimated from our material, but Gram[1] has found that 20 patients on purée diet and iron regenerated on an average in 10 days 15.4% of the deficit (*i. e.*, lowest normal hemoglobin value for the sex minus hemoglobin on admission), or expressed in absolute values, Hg 6.1%. This coincides well with the 5% rise found for our patients in the first 10 days. For patients on purée diet without iron, Gram found a rise of 3.3% hemoglobin in the first 10 days. As will be seen on the curve, patients on ulcer cure showed no perceptible regeneration in the same time. It seems thus—and it is also our impression from a number of patients not quite suitable for comparison in the way here used—that food alone is of definite value for the regeneration of the blood whether or not the effect is supported by giving iron too.

Conclusions. Patients who have lost blood, apparently from peptic ulcer, on full purée diet and iron regenerate their blood much more quickly than those on "ulcer cure." This is well illustrated in the patient who was treated twice for a hemorrhage of about the same degree of severity. This applies especially to the hemoglobin regeneration, as patients regenerate their blood with a lower color index on the ulcer cure than on the purée diet.

Besides the subjective better feeling of the patients, and the better clinical improvement, obvious to both doctors and nurses, but not to be expressed in figures, the better regeneration of the blood supports the lower mortality in maintaining the superiority of the Meulengracht[2] treatment over the old ulcer cure in patients with bleeding ulcer. As in Whipple and his coworkers'[3] experiments on dogs, adequate food has proved its value in regeneration of the blood. These observations do not indicate whether or not some elements in food given are more effective than others, nor whether the effect depends more on quantity than on quality.

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EXPERIMENTS WITH "DEPEPSINIZED" HUMAN GASTRIC JUICE IN THE TREATMENT OF PERNICIOUS ANEMIA.

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In 1932 Roger Morris and associates[1] announced that they had demonstrated in normal gastric juice a "specific hematopoietic hormone" capable of producing, when parenterally administered, significant remissions in pernicious anemia. The gastric "hormone" hypothesis set forth in this and subsequent papers[2,3] was criticized by Minor and Castle[4] and others.[5,6,7] Intramuscular injection of gastric juice might result in a "specific reaction" between the "intrinsic factor" of the juice and the muscle tissue of the recipient. Furthermore, the irritant action of injected gastric juice might result in a purely non-specific hematopoietic stimulation (comparable to that of arsenic), which, if true, would prove nothing as to its alleged hormonal nature and nothing as to a specific relationship with the disease.

It may be important to point out that in the reports of Morris and his co-workers there are only two really significant responses recorded from the injection of human gastric juice—the rest being the results of injection of swine gastric juice obtained by a method not described (presumably "pressed" stomach of slaughtered animals). Can it be that this swine gastric juice was extracted from animals not sufficiently fasted to remove all possibility of specific interaction products? Even if these animals were properly fasted, it might be that the "pressed" juice would represent nothing more nor less than a sort of liquid "ventriculin."

Later workers either completely failed to duplicate Morris' results (Wilkinson[5] and Vlados[6]) or obtained somewhat different results pointing to a different interpretation (Fouts and Zerfas[7]). The later workers found that fresh gastric juice was inert and that ice-box storage for 2 months or more resulted in the development of some degree of potency apparently from some kind of slow "interaction" within the stored juice.

More recently Greenspon[8] presented evidence purporting to prove that the "antipernicious anemia factor" in the stomach (Castle's intrinsic factor) is the only fundamental one and that no extrinsic

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or food factor and no interaction product need be considered. Greenspon's experiments led him to conclude that pepsin is antagonistic to this intrinsic factor, which may preserve its potency outside the living organism (*a*), only if protein is present to adsorb pepsin and thus prevent alleged peptic destruction of the intrinsic factor, or (*b*), if other means such as alkalinization, chilling, and isoelectric precipitation of pepsin are employed to inhibit pepsin or remove it from the field of action.

Greenspon's experiments, as reported, do not seem to be entirely conclusive. His ventriculin experiment is difficult to criticize. It should be pointed out, however, that according to Greenspon, since "ventriculin contains native pepsin" the addition of extra pepsin would seem to be unnecessary for the inactivation of ventriculin if optimum acidity, moisture, and temperature conditions were provided. We plan to test this corollary of Greenspon's thesis which, if true, would tend to strengthen rather than weaken his apparent proof of the destructive action of peptic activity on ventriculin.

Greenspon's next experiments with his preparation of "depepsinized" hog gastric mucosa certainly seem to constitute good grounds for his conclusion that "peptic activity destroys the antipernicious anemia principle and that hydrochloric acid alone does not." Greenspon's observations (on 2 cases) must be extended and confirmed, however, before one can exclude the possibility of other factors having been responsible for the observed results.

His final experiments with the feeding of normal human gastric juice, "peptically inactivated," and with the parenteral injection of concentrates of normal "depepsinized" human gastric juice to patients with pernicious anemia are of especial interest and importance. The criticisms that come to mind regarding these experiments, as reported, are as follows: 1st, the normal human gastric juice donors should have been submitted to at least a 12-hour fast and gastric lavage should have then immediately preceded the collections to eliminate as far as possible all food residues and, 2d, the pernicious anemia recipients of this normal gastric juice, although treated "in the morning on an empty stomach," should have also received gastric lavage before the administration of the juice and should have again received gastric lavage before any food was allowed "4 hours later"—which is too brief a fast-period as Minot has pointed out.*

We have attempted to review some of Greenspon's experiments with these "criticisms" in mind. Although our work, to an even greater extent than his, is open to the objection of "too few cases" and "insufficient observations," it seems none-the-less worth recording as a small part of the data which must eventually be collected and sifted before any sound conclusions can be reached.

* Personal communication.

Methods. The 3 patients with pernicious anemia used in this study were proven cases, in relapse, with red cell counts between 1.4 and 2.3 million and hemoglobin values from 40 to 58% (Sahli). These patients were hospitalized on a meat, broth and iron-free diet during the course of these studies.

Gastric Juice Concentrates for Parenteral Administration. "Depepsinization" of gastric juice was carried out by the method of Fenger and Andrews[9] as recommended by Greenspon.[8] The gastric juice concentrate use in Experiment 1 was prepared in as close accordance with the latter's technique as his brief description of the process permitted. In subsequent experiments (5, 6 and 7), Greenspon's method was closely followed except that after isoelectric precipitation of pepsin and its removal by centrifugalization, the clear supernatant fluid was poured into large pans and reduced to a moist flaky residue by exposure to a current of air never exceeding 33° C. in temperature. This method was found simpler and more rapid than concentration *in vacuo*. The moist residue was then taken up in 30 to 50 cc. of distilled water, treated with alcohol and reconcentrated *in vacuo* at 35° to 37° C. to a volume suitable for intramuscular injection. pH values were determined by means of a potentiometer. Each concentrate was tested for sterility.

In Experiments 3 and 4 attempts were made to concentrate gastric juice by lyophilization.[10] This process offers the advantage of intense cold and dryness, both of which inhibit peptic activity.

The acetone soluble fraction used in Experiment 4 was prepared by the addition of acetone to the depepsinized lyophilized concentrate. A dense white precipitate formed and settled out rapidly. The supernatant fluid was concentrated *in vacuo* to 15 cc. and injected. Opportunity to test the acetone-insoluble fraction has not yet occurred.

Normal gastric juice was obtained from ward and clinic patients with normal blood counts, normal gastric acidity and without evidence of tuberculosis, syphilis or other active infection. In all cases the fasting specimens were discarded and thorough lavage with dilute solution of sodium bicarbonate preceded collection of the juice. The secretions were drained for about 3 hours; suction siphonage was employed in most cases and the collecting bottles were packed in cracked ice. Resort was made to histamin stimulation of gastric secretion in "normal" cases only.

It may be incidentally noted that good yields of pepsin were obtained from normal gastric juice (Experiments 4, 5 and 7); however, pepsin was absent (Experiments 1 and 3) or scanty (Experiment 6) in the gastric juice of patients suffering from pernicious anemia. This concurs with the findings of other investigators.[11]

Gastric Juice Preparation for Oral Administration. Gastric juice for "peptic inactivation" and feeding was secured from 4 "normal" patients. Greenspon's technique was followed closely and in addition each fasting donor underwent preliminary gastric lavage.

EXPERIMENT 1. Mrs. F. (Medical clinic record, 3520535), a typical case of pernicious anemia in relapse, was both donor and recipient in this experiment. After preliminary observation and a week of meat-free diet she received an injection of a concentrate (11 cc.) representing an original volume of 200 cc. of fasting "depepsinized" gastric juice obtained from her own stomach during the preceding week. Reticulocyte fluctuation, for 10 days before and 6 days thereafter, varied between 0.2% and 1.3%. We considered this a completely negative result.

This experiment was undertaken with the thought that if Morris'

so-called addisin produced merely non-specific irritation effects rather than true "hormonal stimulation" there would be no *a priori* reason why pernicious anemia juice might not be as effective as normal juice. Our negative response to pernicious anemia juice seemed to be in line with Morris' hypothesis.*

EXPERIMENT 2. This same patient received, after 14 hours' fasting and immediately preceded by gastric lavage, 500 cc. of pooled normal "peptically inactivated" fasting gastric juice by stomach tube. Food was then further withheld for 5 hours and before any food was administered gastric lavage was repeated to remove any possible residue of the instilled juice. Three days later another 500 cc. of similar normal gastric juice was administered by tube with identical precautions. The reticulocyte level showed a slight increase to 4% on the third day after the first gastric juice feeding (*i. e.*, the day of the second gastric juice feeding). This reached a peak of 5% one day later and then subsided to less than 1% during the following 6 days. At the end of this experiment, 6 days after the second gastric juice feeding, the hemoglobin, red cell count and reticulocytes were a trifle lower than before any of these experiments were begun. This patient's blood picture throughout was in the neighborhood of 1,800,000 red blood cells and 45% hemoglobin. Subsequently (6 days) a reticulocyte rise to 8.2% was obtained from an experimental fraction of liver extract furnished by and administered at the request of Dr. Randolph West. Finally, after this reticulocyte wave had partially subsided, and hemoglobin regeneration was well underway, parenteral administration of a known potent commercial liver extract produced a slight secondary reticulocyte response (8.5%) which was followed by the usual complete hematologic recovery characteristic of Addisonian anemia. Dr. West's fraction was apparently a potent one, because 11 days after its administration the hemoglobin had increased from 40 to 62% (Sahli).

Conclusions. There was a questionably significant rise in reticulocytes which reached a peak on the fifth day after gastric juice feeding was initiated. This was followed by little or no change in the patient's red cells and hemoglobin during the following 2 weeks. We interpret this as uncertain evidence of a minimal response. The normal gastric juice which apparently produced this questionable response was pooled material less than 4 days old and treated throughout according to Greenspon's technique.

We cannot accept this evidence as proof of anything. We have not infrequently observed spontaneous reticulocytosis of this magnitude. Furthermore, even though we took special precautions to to exclude food factors from both donor and recipient, it is obvious

* This experiment, carried out during February, 1936, was similar to one reported subsequently by Goldhamer.[12] Incidentally our result differs from Goldhamer's in that he obtained what he considered to be evidence of some intrinsic factor in the pernicious anemia gastric juice which he employed.

that prolonged starvation of both would be necessary to approximate this objective.

EXPERIMENT 3. Mr. Q. (Medical Clinic record, 304100). a typical case of pernicious anemia in relapse, was the recipient and in part the donor too in this experiment. An attempt was made to concentrate gastric juice from 3 pernicious anemia patients in relapse by lyophilization. Owing to difficulty in securing a sterile finished product* the contaminated lyophilized concentrate of an original amount of 248 cc. of pernicious anemia gastric juice was subsequently pooled with 130 cc. of fresh similar pernicious anemia juice and the mixture concentrated (and incidentally sterilized) by the method used in Experiment 1. The finished concentrate, amounting to 10 cc. (derived from 378 cc. of pernicious anemia gastric juice), was injected. The patient developed a rather severe local and systemic reaction. The highest pre-treatment reticulocyte figure during 2 weeks' preliminary observation was 2.1%. The day after the injection the reticulocytes numbered 3%. Subsequently there occurred a slight wave of reticulocytes which reached a peak of 4.7% on the twelfth day after the injection. During this period, however, the red cells and hemoglobin declined moderately and the patient was clinically worse.

Our conclusions from this are identical with those on Experiment 1. We obtained no evidence of activity from pernicious anemia gastric juice injections. We are inclined to believe that the slight reticulocyte rise noted in this experiment was not significant. The process of "lyophilization" employed in this and the following experiment may make them inadequate "controls" as far as Greenspon's, Goldhamer's and Morris' techniques are concerned.

EXPERIMENT 4. This same patient received (intramuscularly) a concentrate (11 cc.) of the acetone soluble fraction of lyophilized normal fasting human gastric juice representing an original volume of 600 cc. On the fourth day following this injection the reticulocytes rose from a pre-injection level of 1.4% to 3.5% and then declined to the pre-injection level. A week later the patient's red cells and hemoglobin were unchanged.

Conclusions. Either lyophilization destroyed the (alleged) hematopoietic activity of the normal "depepsinized" gastric juice employed in this experiment or none was present in this fraction.

EXPERIMENT 5. This same patient was given (intramuscularly) a concentrate (12 cc.) representing an original volume of 700 cc. of normal "depepsinized" fasting human gastric juice obtained during the preceding week. The highest reticulocyte figure after this injection was on the fourth day (2.3%) and 20 days after the injection the red cell count and hemoglobin were unchanged (1.9 million and 45% respectively). At this juncture potent liver extract injections produced, after 6 days, a reticulocyte crisis of 29%.

* The process of lyophilization does not sterilize previously contaminated material.

Conclusions. This experiment fails to confirm the results of Greenspon and incidentally of Morris and co-workers and of Conner.[13]

EXPERIMENT 6. Mr. S. (Medical Clinic record, 3622319) was a typical case of pernicious anemia in relapse. Throughout a preliminary period of observation of 12 days in the ward on a meat-free diet the red cells and hemoglobin were constantly in the neighborhood of 1.9 and 40% respectively. The reticulocytes, however, showed a slight spontaneous rise from an average of 1% to a peak of 5.4% without any treatment. After this spontaneous reticulocyte wave had subsided the patient received a parenteral injection of 10 cc. of his own concentrated "depepsinized" gastric juice representing a total volume of 320 cc. collected during the preceding 10 days. Following this injection, by 4 and 8 days respectively, there were two peaks of reticulocytosis of 4.5% and 5.3% each, without any significant change in the rest of the blood picture or in the clinical condition of the patient.

Our conclusions from this experiment are similar to those in Experiment 1 (and 3). We thought it best in these experiments with pernicious anemia gastric juice to follow Greenspon's directions regarding the inactivation and removal of pepsin, even though we could demonstrate little or no pepsin in the specimens obtained from our pernicious anemia patients.

EXPERIMENT 7. This same patient received a concentrate (10 cc.) representing an original volume of 500 cc. of normal depepsinized fasting human gastric juice collected within the preceding week. During the following 8 days the reticulocytes did not go above 2.4% which is less than had been previously noted during the control period. Subsequently potent commercial liver extract injections were followed by the typical hematologic and clinical recovery characteristic of Addisonian anemia. The patient was uncoöperative and left the ward after 6 days of potent liver therapy when his reticulocyte rise was well underway (12%) but before the peak. Three weeks later his hemoglobin was 84% and red cells were 4 million.

Conclusions. This experiment failed to confirm the results of Greenspon and Morris.

Discussion. Contrary to the results of Goldhamer,[12] we obtained no conclusive evidence of the presence of "intrinsic factor" in pernicious anemia gastric juice obtained from and readministered to 3 patients in relapse phase (Experiments 1, 3, and 6). These negative results might be interpreted as evidence against the "non-specific irritation" hypothesis advanced by Castle and Minot to explain Morris' results with so-called addisin. No conclusions, however, may be drawn because we failed also to obtain a significant response from similar injections of normal gastric juice concentrates (Experiments 4, 5 and 7).

Contrary to the results of Morris and co-workers, we obtained no significant responses from intramuscular injections of normal fasting human gastric juice concentrates administered to two differ-

ent patients in relapse phase of pernicious anemia. Our concentrates of normal juice were prepared according to Morris' technique plus the "depepsinizing" procedures of Greenspon in most instances (Experiments 5 and 7). In one instance in this normal juice group, however, we tried a "lyophilized" concentrate (Experiment 4), which was equally ineffective. In no instance in this series of experiments did we observe the marked leukocytosis, the nucleosis, or the increase of nuclear particles in red cells reported by Morris and Greenspon. Platelet increase was observed in one instance (Experiment 3).

Contrary to the results of Greenspon we obtained no conclusive responses from either the feeding (Experiment 2) or the injection (Experiments 5 and 7) of "depepsinized" normal fasting human gastric juice, prepared according to Greenspon's description, but obtained and administered with rigid care to exclude as far as possible extrinsic food factors in both donors and recipients. While our experiments do not actually disprove any of the conclusions of Morris or Greenspon, and particularly do not touch seriously upon Greenspon's apparent demonstration of peptic antagonism toward intrinsic factor (which we are not prepared to question on the basis of our work), they do cast doubt upon their hypothesis in so far as it excludes Castle's "extrinsic factor" and "interaction products."

Summary. 1. In 3 patients in relapse phase of pernicious anemia intramuscular injections of "depepsinized" concentrates of fasting gastric juice obtained from themselves failed to produce significant reticulocyte responses.

2. In 1 patient in relapse phase of pernicious anemia the oral administration (of 1000 cc. in 2 doses) of "peptically inactivated" normal fasting human gastric juice failed to produce a truly significant reticulocyte response (*i. e.*, no greater reticulocytosis than we have observed to occur spontaneously in relapse phases of pernicious anemia).

3. In 2 patients in relapse phase of pernicious anemia the intramuscular injection of depepsinized normal fasting human gastric juice concentrates failed to produce significant reticulocyte responses.

Conclusions. Our experiments fail to substantiate the results and hypotheses of Morris and co-workers and of Greenspon, as regards the sole importance of "intrinsic factor." While entirely negative, our experiments constitute no grounds for disbelief in Castle's fundamental "conditioned deficiency" concept of pernicious anemia. We believe that Greenspon, although possibly right in his conclusion that peptic digestion destroys "ventriculin," has not proven the rest of his hypothesis regarding the complete unimportance of Castle's "extrinsic" factor and "interaction product" mechanisms.

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THE EFFECT OF AMIDOPYRIN UPON THE RED, WHITE AND POLYMORPHONUCLEAR BLOOD CELLS OF A SERIES OF 100 PATIENTS.

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In a previous paper,[1] 2 patients were reported with agranulocytosis which developed during the routine administration of amidopyrin. My first cases of agranulocytosis attributed to amidopyrin medication were observed on February 4, 1933 (reported at the February Staff Conference of this hospital) and in June, 1933. Both were reported before the Clinical Society of the New York Polyclinic Medical School and Hospital in November, 1933. Since that time, 2 more cases have been observed in private practice and 2 others in consultation.

The literature on the subject is now voluminous. To date, however, there has not appeared any statistical analysis of the effect of amidopyrin upon the hematologic findings of a large series of patients. Although divergent views on the subject exist, it is believed that enough evidence has been published to indicate that amidopyrin bears some causal relationship to agranulocytosis.

A review of the literature is unnecessary, because this was recently analyzed by Kracke,[2] who collected reports of 172 cases attributed to drug therapy, of which 153 were probably caused by amidopyrin.

Vaughan[3] showed that the ingestion of food to which a patient is sensitive may produce leukopenia. This, however, involves all of the white blood cells and is not a true agranulocytosis. Squier and Madison[4] demonstrated skin sensitivity to amidopyrin by patch testing of 2 or 3 patients who had recovered from agranulocytosis. On the other hand, Benjamin and Biederman,[5] using patch methods, found no evidence of the allergic state in their patients. Taussig[6] reported a case of urticaria developing after a 5-gr. dose of amidopyrin, although a few months previously the patient had taken it without any toxic effect. The author has observed 3 cases of urticaria which developed during amidopyrin medication. In these cases, the urticaria appeared after only a few doses of amidopyrin. The exact method by means of which amidopyrin acts to produce agranulocytosis is still in doubt. Kracke[2] discussed the different theories and the reader is referred to his monograph for a more detailed report.

The present study was undertaken to determine (1) the frequency of the occurrence of agranulocytosis in a series of 100 patients treated with amidopyrin, and (2) any change in the red and white blood cell counts, or polymorphonuclear counts, of patients who were treated with amidopyrin but did not develop agranulocytosis. This was done in an effort to determine if agranulocytosis might be due to drug idiosyncrasy or if leukocytic changes occur with any regularity during the course of amidopyrin medication.

In some cases, magnepyrin, a preparation containing a mixture of amidopyrin (2½ gr.) and magnesium carbonate (4 gr.), was used, usually 3 or 4 of these tablets being administered daily for varying intervals. The other patients were given amidopyrin (5 gr.), 3 or 4 times daily. The patients each received a mean daily dose of 13.08 gr. and a mean total amount of 1098 gr. of amidopyrin during a mean interval of 84.36 days.

Patients with rheumatoid and miscellaneous arthritis (including mixed and osteoarthritis) were selected for study whenever they were admitted to the clinic. A complete blood count, sedimentation rate and nuclear count was made on each patient about every 7 to 10 days. The laboratory data used for statistical study were (*a*) the white blood cell count, (*b*) the red blood cell count, and (*c*) the polymorphonuclear count.

The cases were divided into the following five groups according to the sex and type of arthritis: Group 1, males with rheumatoid arthritis; Group 2, females with rheumatoid arthritis; Group 3, males with miscellaneous arthritis; Group 4, females with miscellaneous arthritis; and Group 5, the 100 cases as a whole.

Frequency of the Development of Agranulocytosis in Patients Receiving Amidopyrin Medication. During the past 3 years, over

100,000 tablets of amidopyrin, or amidopyrin mixed with magnesium carbonate, were administered to 400 patients in the clinic and in private practice. Of these, 4 (1%) (1 male and 3 females) developed agranulocytosis and 3 of them died. Although this incidence is small, it is important because of the high mortality rate.

The male (aged 48) and 1 female (aged 33) had severe rheumatoid arthritis of long standing. The other females (aged 69 and 75) had osteoarthritis. Thus it appears that the agranulocytic syndrome usually occurs in elderly people or in those with long-standing infection. Therefore, amidopyrin is never given to patients over 60, or to those with long-standing infection, *e. g.*, rheumatoid arthritis with loss of weight, poor appetite, anemia, etc. Amidopyrin does not appear to affect the younger patients who do not have these complications.

TABLE 1.—ANALYSIS OF VARIATIONS IN THE 4 GROUPS.

Group.	Type.	No.	Cells.	P.E. of dif.	Dif.	$\frac{Dif.}{P.E.}$	Result.
1	Males with rheumatoid arthritis	12	Lck.	±809.6	−557	0.690	Not significant.
			Polys.	±2.7031	−3	1.147	Not significant.
			R.B.C.	±123.690	+500,000	4.043	Significant (more than 3 × P.E.).
2	Females with rheumatoid arthritis	32	Lck.	±362.9	+1,028	2.800	Prob. significant.
			Polys.	±1.439	+1	0.695	Not significant.
			R.B.C.	±69.935	+80,000	1.159	Not significant.
3	Males with miscellaneous arthritis	17	Lck.	±523.9	−107	0.200	Not significant.
			Polys.	±1.9587	+5	2.552	Doubt. significant.
			R.B.C.	±119,220	+160,000	1.342	Not significant.
4	Females with miscellaneous arthritis	39	Lck.	±325.5	+104	0.320	Not significant.
			Polys.	±1.2033	−3	2.552	Doubt. significant.
			R.B.C.	±73,783	+110,000	1.490	Not significant.
All cases		100	Lck.	±225	+290	1.289	Not significant.
			Polys.	± .8338	− .58	.688	Not significant.
			R.B.C.	±44.559	+155,790	3.5	Significant.

In 5 other patients, the white blood cell count was reduced from about 5000 to about 3000 and the polymorphonuclear count was reduced from approximately 50 to 35%. On the other hand, an occasional initial polymorphonuclear count of about 35% was increased to about 55% with a coincident rise in the white blood cell count. Since a low white blood cell count and polymorphonuclear cell count existed in a few patients, the above-mentioned reductions in the white blood cell count were not considered significant.

Analysis of 100 Cases. (Exclusive of 4 that developed agranulocytosis.) The following standard formulas as published by Kent[7] have been used in the calculations. Group 2 data are used for illustration.

Standard Deviation.

$s = \sqrt{\frac{S(X^2)}{N}}$, where s = standard deviation, S = the sum, X^2 = the squares of the individual deviations from the mean, and N = the number of values in the series, or:

$$s = \sqrt{\frac{\text{sum of the squares of the individual deviations from the mean}}{\text{number of cases}}}$$

If x = the initial determinations and y = the final determinations, then substituting the values of the white blood cell counts in Group 2, we have: $S_x = \sqrt{\frac{107,616,900}{32}} = \sqrt{3,363,028} = \pm 1833.8$, which is the standard deviation of the initial white blood cell counts.

Likewise, $S_y = \sqrt{\frac{169,826,000}{32}} = \sqrt{5,307,060} = \pm 2303.8$, which is the standard deviation of the final white blood cell counts.

Probable Error of the Mean. Using the above symbols, the probable error of the mean (PE_m) is calculated as follows: $PE_m = 0.6745 \times \frac{S}{\sqrt{N}}$. Substituting the values of the white blood cell counts, $PE_{mx} = 0.6745 \times \frac{1833.8}{\sqrt{32}} = \pm 218$, which is the probable error of the mean of the initial white blood cell counts. Likewise, $PE_{my} = 0.6745 \times \frac{230.38}{\sqrt{32}} = \pm 274$, which is the probable error of the mean of the final white blood cell counts.

Probable Error of the Difference. Pearl[8] states that "The probable error of the difference between any two independent quantities (*i. e.*, quantities such that there is no correlation between their errors) is equal to the square root of the sum of the squares of the probable errors of the quantities entering into the difference," or: $\sqrt{(PE_mX)^2 + (PE_mY)^2}$ = the probable error of the difference, where X and Y are the independent quantities entering into the difference. In the present instance X = the initial and Y the final white blood cell counts. Substituting the values of the white blood cell counts: $\sqrt{(218)^2 + (274)^2} = \pm 362.9$, which is the probable error of the difference. According to Pearl,[8] "It has been practically a universal custom among biometric workers to say that a difference (or a constant) which is smaller than twice its probable error is probably not significant, whereas a difference (or a constant) which is three or more times its probable error is either 'certainly' or 'almost certainly' significant." The difference equals the difference between the initial mean white blood cell count and the final mean white blood cell count, or +1028. Therefore, $\frac{1028}{362.9} = 2.8$, or the difference is over twice the probable error of the difference. Although this difference is slightly less than 3, the value, Pearl[8] says, is certainly significant; it so closely approximates this number that it might be considered a significant increase.

The above methods of calculation are used throughout this analysis.

Discussion. When the series of 100 cases is considered as a whole, the only change noted is a significant increase in the red blood cell counts. When, however, the groups are analyzed separately, there is a definitely significant increase in the red blood cell counts in males with rheumatoid arthritis, a significant increase in the white blood cell counts of the females with rheumatoid arthritis and a possible significant decrease in the polymorphonuclear counts in females with miscellaneous arthritis. It is interesting to note that the red blood cell counts are increased in all groups and that no definitely significant hematologic decrease occurred in any group. From this, it might be maintained that agranulocytosis developing during the course of amidopyrin medication must be due to an individual hypersensitivity or idiosyncrasy.

Conclusions. Exclusive of 4 patients who developed agranulocytosis, there was no appreciable change in the white blood cell counts or polymorphonuclear counts of 100 patients who were given amidopyrin daily for prolonged periods.

There was a significant increase in the red blood cells.

Agranulocytosis developed in 1% of 400 patients who were given amidopyrin medication.

It is concluded that amidopyrin does not produce hematologic changes, except in certain isolated cases where there is probably an idiosyncrasy toward the drug.

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THE RELATION BETWEEN THE SUSPENSION STABILITY OF ERYTHROCYTES AND VARIOUS CONSTITUENTS OF PATHOLOGIC HUMAN BLOOD.*

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In health the suspension stability of the blood is maintained with remarkable constancy. In disease it is diminished so that the erythrocytes separate from the plasma with varying degrees of rapidity. What is the cause of the increased rate of erythrocyte sedimentation?

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Fahraeus[1] concluded that the increased sinking velocity of the red blood corpuscles depends upon: (1) An increased agglutination of the corpuscles, and (2) on a diminution in their number. In a series of experiments in which he used horse blood proteins he showed that the "agglutination capacity of the plasma" was the primary factor in producing a rapid sedimentation of erythrocytes. He also showed that the most rapid sedimentation and, therefore, the maximum agglutination, took place in solutions of fibrinogen, the less rapid in solutions of globulin, and the least rapid in solutions of albumin. He further showed that there was no relation between the sedimentation rate and the total plasma proteins. In a second publication[2] he stated that the phenomena of increased sinking velocity of the red blood corpuscles and the increased percentage of serum globulin and fibrinogen occurring coincidently, "stand in direct causality."

Westergren[3,4] concluded that there was a definite correlation between the plasma or serum proteins and the rate of sedimentation of erythrocytes. *This rate is defined in millimeters of drop per hour of time.* From a series of 100 analyses, Westergren selected the middle 62 for statistical study. When he plotted the values for the various blood proteins against the sedimentation rate these appeared to fall along a straight line. Westergren's values for the correlation coefficients between fibrin, globulin, albumin and the sedimentation rate are shown in Table 1, p. 181.

Since Westergren's original data were published it has been considered advisable to subject them in their entirety to statistical analysis. The data were complete in 97 instances. Correlation coefficients, correlation ratios and partial correlations were calculated.* The results are shown in Table 2, p. 181.

* The correlation coefficient used in this study is that of Karl Pearson, $r_{xy} = \frac{\Sigma_{xy}}{n\sigma_x\sigma_y}$. (Yule, G. U.: An Introduction to the Theory of Statistics, 10th ed., London, Charles Griffin & Co., p. 173, 1928.) It measures agreement or disagreement between two variables in terms of variations from their respective means. *It does not measure cause and effect*, although this conclusion may be reached by the investigator in the interpretation of his results.

The correlation ratios, $\eta_{xy} = \frac{\sigma_{mx}}{\sigma_x}$, $\eta_{yx} = \frac{\sigma_{my}}{\sigma_y}$ (Ibid., p. 205), measure the approach of values of x associated with given values of y (or *vice versa*) to a single-valued relationship of any form, not necessarily linear as is the case of the Pearson correlation coefficient. The difference between $\eta_{xy}^2 - r_{xy}^2$ is a measure of the divergence from linearity of the regression of x on y.

The partial correlation coefficient is used when three or more variables have been intercorrelated, using $r_{xy} = \frac{\Sigma_{xy}}{n\sigma_x\sigma_y}$, and when one or more of these variables is held constant in order to determine their influence on the relationships established. If there were three variables, x, y and z, and it was desired to test the influence exerted by z on r_{xy}, z could be rendered constant by using the following formula for partial correlation, $r_{xy.z} = \frac{r_{xy} - r_{xz} \cdot r_{yz}}{\sqrt{1 - r_{xz}^2} - \sqrt{1 - r_{yz}^2}}$. (Ibid., p. 239.)

TABLE 1.—CORRELATION COEFFICIENTS BETWEEN SEDIMENTATION RATE, FIBRIN, GLOBULIN, ALBUMIN AND TOTAL PROTEIN. (COMPILED FROM WESTERGREN.)

r_{SR-F}	$= +0.82$	r_{SR-TP}	$= +0.15 \pm 0.12$
r_{SR-F}*	$= +0.85$	r_{F-G}	$= +0.34$
r_{SR-G}	$= +0.50$	r_{F-A}	$= -0.30$
r_{SR-A}	$= -0.46$	r_{G-A}	$= -0.42$
r_{SR-FGA}	$= +0.87$		

* n = 97, all others n = 62. SR = sedimentation rate. F = fibrin. G = globulin. A = albumin. TP = total protein.

TABLE 2.—MEASURES OF RELATIONSHIP BETWEEN SEDIMENTATION RATE, FIBRIN, GLOBULIN AND ALBUMIN. (CALCULATED FROM WESTERGREN'S DATA.)

	Correlation coefficient.	Correlation ratios.	
		η_{xy}.	η_{yx}.
SR–F	+0.85	0.87	0.89
SR–G	+0.60	0.64	0.64
SR–A	−0.50	0.58	0.64
F–G	+0.54	0.56	0.58
F–A	−0.43	0.54	0.46
G–A	−0.56	0.57	0.62

TABLE 3.—COEFFICIENTS OF PARTIAL CORRELATION BETWEEN SEDIMENTATION RATE AND FIBRIN, GLOBULIN AND ALBUMIN. (CALCULATED FROM WESTERGREN'S DATA.)*

Zero order correlation coefficients.	First order partial correlation coefficients.	Second order partial correlation coefficients.
$r_{SRF} = +0.85$	$r_{SRF \cdot G} = +0.78$	$r_{SRF \cdot GA} = +0.77$
	$r_{SRF \cdot A} = +0.81$	
$r_{SRG} = +0.60$	$r_{SRG \cdot F} = +0.34$	$r_{SRG \cdot FA} = +0.26$
	$r_{SRG \cdot A} = +0.46$	
$r_{SRA} = -0.50$	$r_{SRA \cdot F} = -0.30$	$r_{SRA \cdot FG} = -0.18$
	$r_{SRA \cdot G} = -0.24$	

* All coefficients are significant in terms of their probable errors, except $r_{SRA \cdot FG}$.

The data in Tables 2 and 3 show:

1. The values of the correlation coefficients between sedimentation rate and fibrin, globulin and albumin, respectively, when the total number of cases is studied, agree with Westergren's findings as published for the selected sample.

2. By calculating correlation ratios it was found that these are not significantly higher than the correlation coefficients. It may be assumed, therefore, that the relationships between sedimentation rate and the various serum proteins are linear.

3. By calculating the partial correlations upon which the multiple coefficient ($r_{SR \cdot FGA}$) depends, it was found that the increase in sedimentation rate and the increase in the amount of fibrin are closely related even when globulin and albumin are rendered constant, but that an increase in globulin is not correlated to any appreciable extent with rapidity of sedimentation after the influence of fibrin is rendered constant. The negative correlation between sedimentation rate and albumin (−0.50) seems to depend entirely upon the *negative* relationship between albumin and fibrin

and albumin and globulin, because, when fibrin and globulin are rendered constant the correlation is reduced almost to zero.

4. These findings explain the high multiple correlation coefficient (0.87) which Westergren obtained between sedimentation rate and fibrin, globulin and albumin when taken collectively. The increase in the multiple correlation coefficient of only 0.05 over the highest zero order correlation coefficient (0.82 between sedimentation rate and fibrin, Table 1) indicates that the globulin and albumin play little, if any, part in establishing the positive multiple correlation. It must also be pointed out that the correlation coefficient between sedimentation rate and albumin is negative, as are also the correlations between fibrin and albumin, and globulin and albumin. The multiple correlation coefficient is always positive in sign and greater than the highest value of any correlation which is contained in its formula.

The following study was undertaken in order to determine what effects variations in the blood serum proteins and blood counts have upon the suspension stability of erythrocytes. The suspension stability is defined as those forces tending to impede the sedimentation of erythrocytes in plasma. *An increase in suspension stability indicates a prolongation in sedimentation time and vice versa.*

Materials and Methods. An attempt was made to obtain samples from hospital patients suffering from a variety of illnesses and exhibiting wide variations in sedimentation time. Samples from normal persons were excluded from this study.

With few exceptions all analyses were done on a single sample of venous blood. In most of the cases the blood counts were done on blood obtained from the finger or ear shortly before or immediately after collection of the sample of venous blood.

All of the sedimentation tests were done as follows: 0.2 cc. of 5% sodium citrate solution was aspirated into a tuberculin syringe, then 0.8 cc. of blood was aspirated and this mixture was thoroughly agitated. The sample of citrated blood, free of air bubbles, was transferred to a Friedlaender tube and the time necessary for the column of erythrocytes to settle 18 mm. was recorded.

The serum protein, globulin and albumin analyses were done by means of the clinical methods of Greenberg.[5]

The hemoglobin was determined by means of a Sahli hemoglobinometer (100% equals 14 gm. of hemoglobin per 100 cc. of blood), and the standard methods were employed for counting erythrocytes and leukocytes.

The data for sedimentation time, total protein, serum albumin, serum globulin, albumin-globulin ratio, red blood corpuscle count, hemoglobin content, white blood cell count and neutrophil count obtained from 102 patients suffering from various diseases were compiled and studied.

Globulin. The correlation coefficient of -0.27 between sedimen-

tation time and globulin content, although of low magnitude, is statistically significant. On the average, when the globulin content is low the sedimentation time is prolonged.

TABLE 4.—MEANS, STANDARD DEVIATIONS AND MEASURES OF RELATIONSHIP BETWEEN SEDIMENTATION TIME AND VARIOUS CONSTITUENTS OF PATHOLOGIC HUMAN BLOOD (102 CASES).*

	Means.	Standard deviations.	Correlation coefficients with sed. time.	Correlation ratios with sed. time.	
				η_{yST}.	η_{STy}.
Globulin	2.54	0.61	−0.27	0.33	0.31
Albumin	3.92	0.79	+0.23	0.28	0.27
A/G ratio	1.62	0.44	+0.43	0.50	0.47
Total protein	6.51	1.10	+0.06	0.24	0.27
R.B.C. count	4.25	0.80	+0.41	0.52	0.58
W.B.C. count	10,658	15,622	+0.26	0.91‡	0.34
W.B.C. count†	10,015	5,845	+0.11	0.25	0.16
Pmn count	68.80	15.50	−0.28	0.55	0.44
Sedimentation time	96.00	117.50			
Sedimentation time†	92.50	112.00			

* All coefficients are significant in terms of their probable errors excepting +0.06, +0.11 and 0.16.

† Case No. 100 omitted (W.B.C. count, 160,000).

‡ This value for η of W.B.C./ST is disproportionately high because of the inadequate distribution which results when arrangements are made to accommodate Case No. 100.

Albumin. The correlation coefficient of +0.23 between sedimentation time and albumin is low but statistically significant. On the average, when the albumin content is high, the sedimentation time is prolonged. The positive correlation of 0.43 between the albumin-globulin ratio and the sedimentation time indicates that, on the average, as the sedimentation time becomes prolonged, the greater the content of albumin relative to globulin.

Total Protein. There is no linear relation between sedimentation time and total protein. The correlation ratios show a low statistically significant value along a curve. This probably depends upon the fact that as the value for the sedimentation time increases above the mean, the total protein, showing less variation, reaches a level around its mean. It must be pointed out that only 8 cases in a total of 102 functioned to produce this effect. It is also interesting that these same 8 cases have red blood corpuscle counts greater than the mean for red blood cell counts.

Red Blood Cell Count. The correlation coefficient of +0.41 signifies that, on the average, as the red blood corpuscle count increases, the sedimentation time also increases and *vice versa.*

White Blood Cell Count. The total white blood cell count bears little, if any, relationship to the sedimentation time. On the other hand, as the sedimentation time increases, the neutrophil count decreases and *vice versa.* This relationship fits a curve better than it does a straight line, as is indicated by the difference between the correlation coefficient of −0.28 and the η_{yST} of 0.55.

Discussion.—From the foregoing presentation of the data of Westergren (Table 3) it *appears* that the sedimentation rate is influenced to a certain degree by the fibrin content and to a much lesser degree by the globulin content of the plasma. To conclude that a cause and effect relationship exists between an increase in the globulins (fibrin and globulin) and an increase in the sedimentation rate is not justifiable. A cause and effect relationship cannot be inferred from our data.

TABLE 5.—VALUES FOR THE PLASMA PROTEINS AND SEDIMENTATION TIME OF THE BLOOD OF HORSES, RABBITS AND MAN.

	Total serum protein.	Albumin.	Globulin.	Fibrin.	Fibrinogen.	Sed. time, min.
Horse[6]	6.95	2.46	3.84	0.65		
Horse[10]	8.04	2.80	4.79	..	0.45	
Horse[7]:						
Age, 1–2.5 yrs.	6.21–7.40	2.22–2.84	3.38–5.22	..	..	15–60
Age, 4–15 yrs.	6.94–8.63	1.82–3.02	3.92–6.13			
Horse[8]	5.76–7.23	3.01–3.27	2.49–4.17	..	0.34	
Man[8]	7.19	4.45	2.73	..	0.30	
Man[10]	7.26	4.01	2.83	..	0.42	180–660
Rabbit[8]	5.55–6.05	4.10–4.47	1.45–1.58			
Rabbit[9]	5.40	3.03	1.86	0.50	..	600–2400

A study of the variations in sedimentation time in relation to plasma and serum proteins in different species reveals that some factor other than the proteins must be responsible for altering the suspension stability of the blood. The blood serum globulin content among the different species does not vary to any great extent, while the sedimentation time which does, appears to be characteristic for each species. The values charted in Table 5 illustrate that the variations in sedimentation time are out of proportion to the variations in the different protein values.

TABLE 6.—VALUES FOR THE PLASMA PROTEINS AND SEDIMENTATION TIME OF THE BLOOD IN NEPHROSIS.

Case.	Total serum protein.	Serum albumin.	Serum globulin.	Sed. time, min.
1	2.76	0.95	1.81	7
2	2.80	1.00	1.80	8
3	3.85	2.40	1.45	16
4	5.48	2.17	3.31	17
5	3.90	2.01	1.70	18
6	4.74	2.20	2.54	30
7	6.30	3.26	3.03	30
8	4.39	2.96	1.55	52

A similar phenomenon may be observed if one studies the variations in the protein and sedimentation time in a series of cases of nephrosis. Here again it is noted that the variations in the sedimentation time is great, while the variation in the globulin content is much less. In addition, the prolongation of the sedimentation time does not parallel the values found for serum globulin.

Fahraeus[1] pointed out that the red blood corpuscles are agglutinated by many substances, including certain colloids and emulsoids and that the rapidity of formation and size of the agglutinated mass of corpuscles bears a certain relationship to the rate of sedimentation.

Lucia and Brown[11] have shown that the suspension stability of erythrocytes is markedly diminished in solutions of gum acacia *in vivo* and *in vitro*. They state that, "although there appears to be an association between an increase in blood serum globulins and a diminished suspension stability, the real causative factor is an agglutinant which may or may not be associated with the globulins."

In another series of *in vitro* experiments it was shown that the suspension stability of erythrocytes was more often increased than decreased in solutions of animal and human blood serum globulins.[12]

Summary. An analysis of the suspension stability of erythrocytes in 102 cases reveals that the sedimentation time is apparently accelerated as the globulin content of the serum increases and is retarded as the albumin content of the serum increases. These correlations, although low in value, are statistically significant. A cause and effect relationship cannot be said to exist between an increase in the blood serum globulin and an acceleration in the sedimentation time.

A diminution in the red blood corpuscle count, or an increase in the neutrophil count, is associated with an increase in the sedimentation time.

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THE RELATIONSHIP BETWEEN ALCOHOLIC INTOXICATION AND ANOXEMIA.*

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Frequent references have been made in studies of anoxemia, on mountain expeditions, altitude flights or in low oxygen chambers, to the similarities in the behavior of a person suffering from oxygen want to one under the influence of alcohol. Barcroft[1] believes that the symptoms of acute anoxia are precisely those of alcoholic intoxication and that "acute oxygen want simulates drunkenness, while chronic anoxemia simulates fatigue." Under both conditions a person may become irrational and uninhibited and lose the capacity for self-criticism, association, memory, sensitivity and motor control. In summarizing the psychological effects of anoxemia McFarland[2] has also pointed out this striking resemblance and in experiments with low oxygen he reported that the most frequent initial remark from naive observers was related to feelings of alcoholic intoxication.

After Y. Henderson[3] discovered that CO_2 caused a more rapid de-etherization after narcosis, Hunter and Mudd[4] reported that patients in coma due to alcohol were improved in some cases to the state of mental clarity following the inhalation of 7 to 10% CO_2 for one-half hour. Palthe[5] found in guinea pigs and rabbits that the loss of control of postural reflexes due to alcohol could be improved by inhaling pure oxygen. In human subjects he observed that acute symptoms of intoxication following excess alcohol could be counteracted with pure oxygen and that delirium tremens patients could be improved with oxygen (with or without 5% CO_2). Recently Robinson and Selesnick[6] reported striking reduction in the venous blood alcohol of inebriates following the inhalation of 90% O_2 and 10% CO_2 for $\frac{1}{2}$ hour. Newman and Card[7] found no significant change however in the total body alcohol of less intoxicated subjects under similar experimental conditions.

Hunter and Mudd attributed the more rapid elimination of alcohol to the increased pulmonary ventilation induced by the CO_2 while Palthe thought the oxygen counteracted the reduced oxygen metabolism of tissue cells produced by the alcohol since the symptoms reappeared if the oxygen mask was removed too soon. Thus it appears that oxygen and CO_2 tend to reduce the symptoms of alco-

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holism. But it is not clear whether this effect is due to a diminution of alcohol in the blood or to a facilitation of the use of oxygen in the tissues.

Himwich[8] has reviewed the evidence relative to elimination of alcohol from the body and to the variables which influence the rate of oxidation. Mellanby[8] says that alcohol is oxidized at a constant rate regardless of the amount present in the body. Haggard and Greenberg[9] take exception to Mellanby's view however, stating that the rate of oxidation is proportional to the amount present. Only a small proportion is eliminated through the lungs, kidneys and skin. For the most part alcohol disappears from the blood after absorption by oxidation in the tissues and supplies a limited amount of energy. Durig[10] found the use of alcohol as a source of muscular energy physiologically unsound in mountain climbing at high altitudes. This finding is in agreement with the observation of Himwich,[11] of an increase in lactic acid following the ingestion of alcohol. According to Carpenter[12,13] the disappearance of alcohol is accounted for in terms of heat and not in energy for bodily use. Contrary to the findings of Voltz and Baudrexel,[14] Carpenter reported that the amount of work in exercise experiments had no significant effect on the rate of oxidation as determined by the respiratory exchange and the amount of alcohol in the expired air, urine and blood. In testing the response of subjects to a standard exercise in air and in high percentages of oxygen with and without alcohol, Barach[15] found that breathing 50% O_2 produced a greater percentage decline in rate of respiration and pulmonary ventilation in exercising subjects who had ingested alcohol than in those who had not.

In following the course of alcohol in the blood of rabbits at sea level and at high altitudes Biehler[16] reported that the concentration decreased with increasing altitude. He attributed this effect to the greater frequency of breathing at high altitudes. Bornstein and Loewy[17] attribute Biehler's results to the fact that the rabbits were not tested under fasting conditions. They found, on the contrary, that the concentration of alcohol in the blood of fasting human subjects rose more rapidly and to a higher level at high altitudes than at sea level. The R. Q. also fell more after the ingestion of alcohol at high altitude than at sea level. McFarland and Forbes[18] in a recent study in the Andes at 17,500 feet confirmed these results. Thus alcohol appears to have greater effect at high altitudes and this may be related to the anoxemia known to exist under these conditions.

Gettler[19] believes that the lower concentration of alcohol one finds in the blood of the habitual drinker as compared to the neophyte is due to increased capacity for oxidation. In experiments with dogs he observed that the ingestion of increasingly greater amounts of alcohol was followed by increased tolerance to theoretically lethal doses.

Various theories have been proposed to account for the symptoms which follow the ingestion of alcohol with general agreement that it is a depressant. Verworn[20] believed that the essential means by which a narcotic acted was through the medium of suppressed oxidation. Warburg[21] has shown that alcohol diminishes the O_2 combining power of red blood corpuscles. Keilin[22] found that alcohol did not prevent the oxygenation of cytochrome (respiratory pigment) in tissue cells, but that it did appear to stabilize the oxcytochrome so that the oxygen could not be removed with normal ease. Quastel[23] believes that all narcotics including alcohol inhibit the oxidation of substances important in carbohydrate metabolism in the brain tissue, viz., glucose, lactic acid and pyruvic acid. Since one of the chief sources of energy of the brain lies in the oxidation of lactic acid, alcohol, according to Quastel, will diminish the supply of energy and hence depress functional activity. In studies of excised brain tissue Robertson and Stewart[24] have shown that alcohol depresses the rate of oxidation by a high degree of absorption on the colloidal surfaces of the oxidative enzyme areas of the brain cells and displaces the more usual metabolites. Since there is no deficit of oxygen in the blood except under conditions of severe shock, the symptoms can be attributed to the inability of the cells to utilize the oxygen in the blood. Such studies led Peters and Van Slyke[25] to classify acute alcoholism as a histotoxic anoxia.

It appears that alcohol is ultimately a depressant and that the effect is related to the impairment of oxidation in the tissues, especially the nervous tissue. It has been demonstrated that excess oxygen and carbon dioxid will improve the well-being and mental clarity of a person suffering from excess alcohol. It is not clear, however, whether the excess oxygen acts by way of the tissues or by lowering the concentration of alcohol and lactic acid in the blood. The present investigation, therefore, has been carried out to determine the extent to which alcohol brings about a condition of anoxia and the extent to which the inhalation of 50 to 60% oxygen and from 0.2 to 10% carbon dioxid will counteract the effects of excess alcohol. The criteria used were: 1, blood lactic acid; 2, blood alcohol and 3, reactions to psychological tests.

Experimental Procedure. The subjects were tested in a Barach portable oxygen chamber, 7 feet high by 8 feet square, where the percentage of oxygen and carbon dioxid, the temperature, and ventilation could be regulated. The ventilation was provided by a motor blower which circulated the air through a tank containing large chunks of ice to cool and dry the air. The temperature was maintained between 65° and 70° F.; the humidity between 40 and 50%. The oxygen and carbon dioxid concentrations were maintained at the desired percentages by running in gas from cylinders outside the chamber. Determinations were made every 15 minutes on a simplified Haldane gas analysis apparatus.

Twenty-three non-drinking, with the exceptions of Mos and Boo, students served as subjects. The average age was 23 years and the average weight

75 kilos. Each subject was given a series of physical efficiency tests including basal metabolism and the Schneider index of neurocirculatory failure. Four of the subjects (Fre, Sor, Wal and Art) had basal rates below −18. All were found to be in good physical condition.

The subjects came to the laboratory in the morning without breakfast. After resting on a bed for 30 minutes they entered the chamber and were given the drink. In the lactic acid series under strictly basal conditions the subjects spent the night near the laboratory and reclined on a bed inside the chamber throughout the experiment. The subjects were unaware of the changes in the oxygen content except in the 5% carbon dioxid series which caused some distress because of the increased rate of respiration.

The alcohol was ingested in doses of approximately 1 gm. per kilo of body weight and diluted in proportions of $\frac{1}{4}$ alcohol to $\frac{3}{4}$ water and orange juice. An attempt was made to disguise the alcohol with oil of orange and oil of juniper. This was difficult since the subjects could frequently detect the alcohol drinks from the controls due to the sensations in the intestinal tract.

Samples of venous blood were taken $\frac{1}{2}$, 1 and 2 hours after the ingestion of the alcohol. In the lactic acid series a control sample was taken before the alcohol drink and care was taken to keep the subject from getting excited or from muscularly exerting himself. Twenty cc. of blood was drawn each time for the alcohol determinations, and 20 cc. for the lactic acid. Duplicates were run in each case. The amount of alcohol in the blood previous to the ingestion of alcohol with this method averages 0.012 gm. per cc. In 5 of our subjects the range was .011 to .014 mg. per cc. (Table 5). Gettler's method[19] was used in determining the blood alcohol and the Freidemann, Cotonio and Shaffer[26] method for lactic acid. The error of the Gettler method is 3 to 5% and the lactic acid method 3%.

Six psychological tests of varying degrees of complexity were given following the ingestion of alcohol to 14 subjects in the following order: 1, Choice Reaction, 2, Digit Symbol, 3, Color Naming, 4, Pursuit Meter, 5, Code Transliteration, and 6, McDougall Dotting test. The Choice Reaction test involved reacting as quickly as possible to one of 5 colored lights by pressing the corresponding key—score in hundredths of a second. In the Digit Symbol test the subject learned a code and wrote down the numbers corresponding to the symbols—score total number of digits transliterated in 4 minutes. The Color Naming test involved repeating as rapidly as possible the names of 400 colors consisting of 5 different colors—score in seconds. The Pursuit Meter involved keeping two pointers directly opposite each other, one pointer being controlled by an irregular cam. The deviations were recorded automatically—score total amount of deviation. The Code test required the subject to transliterate 50 letters as rapidly as possible—score in seconds. The McDougall Dotting test required the subject to mark the middle one of three dots in a row haphazardly spaced and exposed momentarily on a rotating drum—score total number of dots touched.

The respiratory rate, pulse rate and blood pressure were taken at the beginning and end of each experiment except in Part III where the pulse rate was taken every 15 minutes throughout the 2 hours.

PART I. In the first experiment 4 subjects, Wes, Edw, Mos, and Rob, were given the various psychological and physiological tests discussed above after the ingestion of $\frac{3}{4}$, 1 and $1\frac{1}{4}$ gm. of ethyl alcohol per kilo of body weight, approximately 60 cc., 80 cc., and 100 cc. The subjects took the psychological tests while seated at a table in the chamber.

Table 1 and Figure 1 shows the percentage of alcohol in the blood of subjects breathing air and 50% oxygen and 2% carbon dioxid following the ingestion of various alcohol drinks. In comparing the amount of alcohol in the blood after the ingestion of $\frac{3}{4}$ gm. per kilo

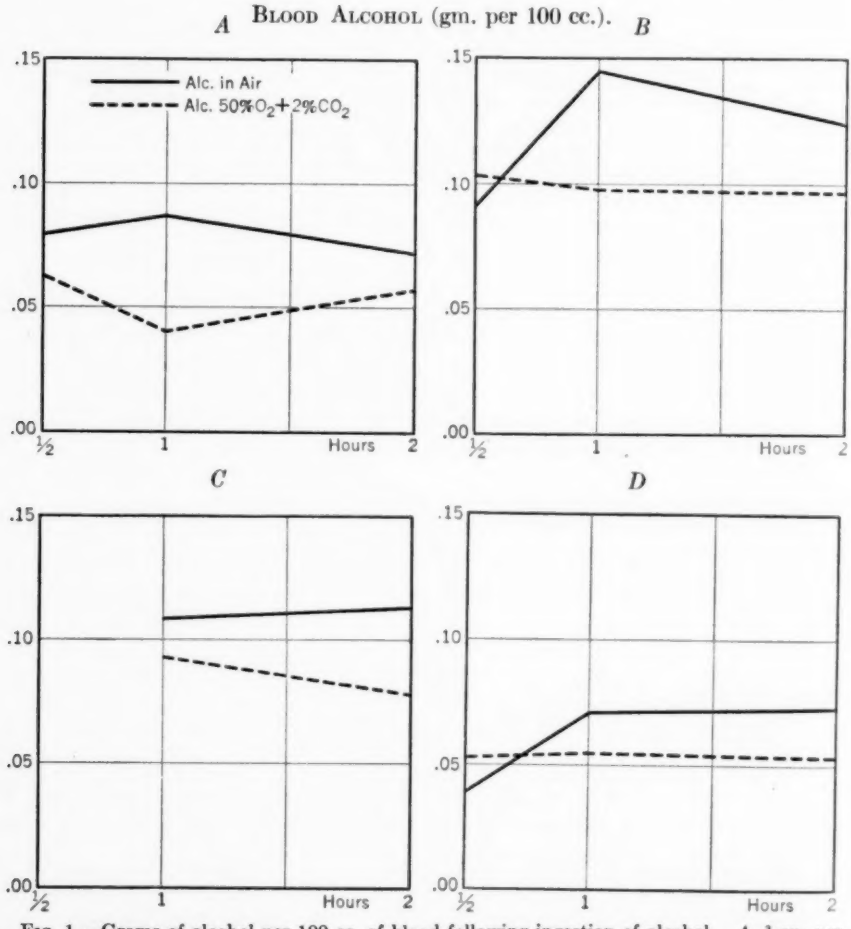

FIG. 1.—Grams of alcohol per 100 cc. of blood following ingestion of alcohol. *A*, $\frac{3}{4}$ gm. per kilo body weight—curves based on averages of 13 subjects; *B*, 1 gm. per kilo body weight—4 subjects; *C*, $1\frac{1}{4}$ gm. per kilo body weight—4 subjects; *D*, $\frac{3}{4}$ gm. per kilo body weight—10 subjects. Basal conditions maintained throughout blood sampling period.

body weight in air with a similar drink in 50% oxygen and 2% carbon dioxid two subjects, Wes and Mos, were not affected and 2 subjects, Edw and Rob, were benefited by the oxygen-carbon dioxid mixture. In the second series with 1 gm. per kilo body weight in high oxygen the blood alcohol determinations were lower in all 4 of the subjects. With the largest drink of alcohol, *i. e.*, $1\frac{1}{4}$ gm. per

kilo body weight, the improvement was very significant after 1 hour in the cases of Wes, Rob, and Mos. In this series the procedure was slightly altered in that each subject breathed mixtures of 80% oxygen and 10% carbon dioxid through a mask for 15 minutes

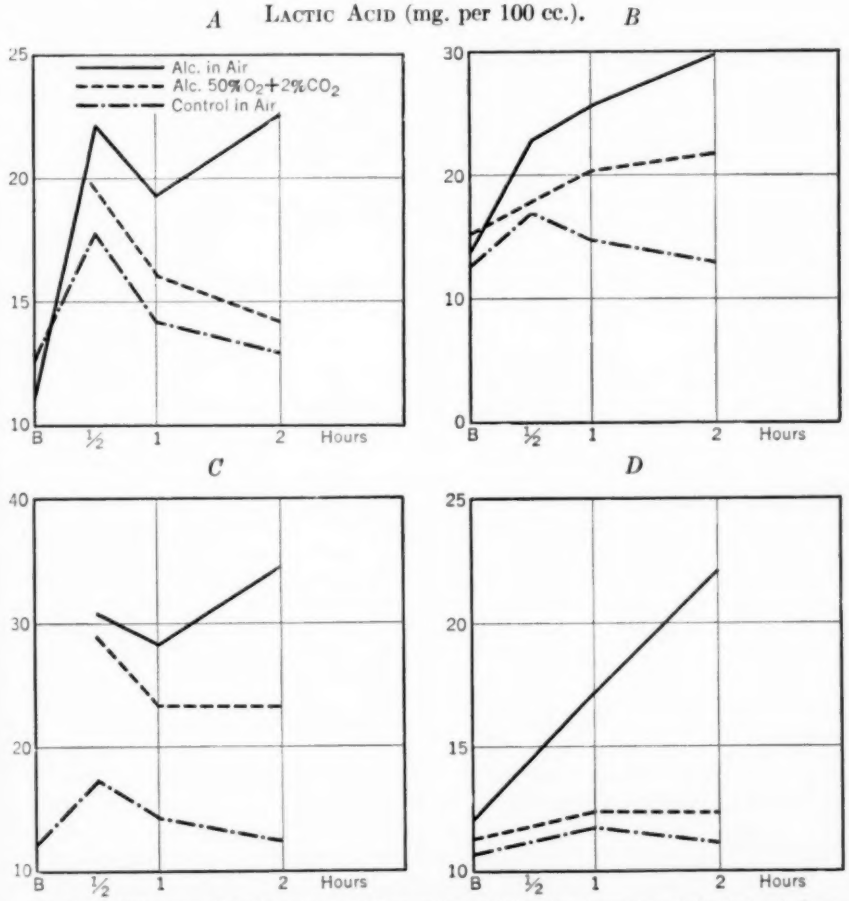

FIG. 2.—Milligrams of lactic acid per 100 cc. of blood following ingestion of alcohol. *A*, ¾ gm. per kilo body weight—curves based on averages of 4 subjects. The alcohol-air curve is based on 9 subjects; *B*, 1 gm. per kilo body weight—4 subjects; *C*, 1¼ gm. per kilo body weight—4 subjects; *D*, ¾ gm. per kilo body weight—5 subjects. Basal conditions maintained throughout blood sampling period.

following the ingestion of the alcohol and previous to entering the chamber. The differences are statistically reliable in the 1 gm. and 1¼ gm. per kilo body weight-series in 50% oxygen and 2% CO_2 as compared to air.

Table 2 and Fig. 2 show the milligrams of lactic acid per 100 cc. of blood just before the drink was taken and ½, 1 and 2 hours follow-

ing the ingestion of the various alcohol drinks as indicated. The increase in lactic acid following the control drink (no alcohol) was negligible. In the 10% oxygen (control drink with no alcohol) as well as following the ingestion of alcohol in air, there were significant increases in the lactic acid. These results are in accord with Himwich,[11] who states that the lactic acid concentration in the blood of human subjects is increased after the ingestion of alcohol. On examination of Table 2 one finds in comparing the lactic acid determinations of subjects breathing high oxygen with the same subjects breathing normal air that the lactic acid is lower in 10 of 12 cases after 2 hours and in 4 of 8 cases after 1 hour.

TABLE 1.—BLOOD ALCOHOL DETERMINATION FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AIR, AND IN 50% O_2 AND 2% CO_2.

Condition.	Period, hours.	Grams per 100 cc. of blood.			
		Wes	Edw	Mos	Rob
¾ gm. alcohol in air	½	.094	.089	.094	.110
	1	.089	.096	.098	.103
	2	.065	.083	.087	.095
¾ gm. alcohol in 50% O_2 and 2% CO_2	½	.089	.086	.096	.118
	1	.085	.080	.097	.091
	2	.065	.076	.085	.075
1 gm. alcohol in air	1	.084	.110	.102	.135
	2	.134	.126	.100	.091
1 gm. alcohol in 50° O_2 and 2% CO_2	1	.128	.093	.074	.079
	2	.103	.077	.062	.071
1¼ gm. alcohol in air	½	.057	.064	.112	.134
	1	.076	.152	.211	.145
	2	.125	.107	.107	.156
1¼ gm. alcohol in 50% O_2 and 2% CO_2	½	.058	.107	.113	.121
	1	.052	.093	.109	.107
	2	.050	.089	.121	.098

PART II. Because there was a certain amount of movement involved in taking the psychological tests, a second series of lactic acid determinations was made on 5 subjects, Wes, Mos, Wal, Kne, and Rob, under strictly basal conditions. They reclined on a bed for an hour outside the chamber and after taking the first sample of blood they entered the chamber and laid quietly on the bed for the 2-hour period. In each case a sample of blood (20 cc.) was taken before the control or the alcohol drink and also 1 hour and 2 hours later. The results are shown in Table 3 and Graph D of Fig. 2. In the control series (no alcohol) there was no significant increase in lactic acid during the 2-hour session. After the ingestion of ¾ gm. of ethyl alcohol per kilo of body weight, all 5 subjects tested in air showed an increase in lactic acid which was verified on 2 subjects, Wal and Kne, on a repeated test. Later the 5 subjects took a similar drink in the chamber filled with 50% oxygen—2% carbon dioxid. Basal conditions were maintained throughout the experiment. With the exception of Kne there was a slight increase in each case, but

significantly less than in air. The series was repeated on Wal and Kne as in the previous series in alcohol and air and the results were verified. The average lactic acid determination was significantly greater for all 5 subjects while breathing air compared with 50% oxygen and 2% carbon dioxid. That is, the chances were 98 to 99 in 100 that the differences were reliable.

TABLE 2.—LACTIC ACID DETERMINATIONS AFTER THE INGESTION OF DILUTED ETHYL ALCOHOL IN AIR, AND IN 50% O_2 AND 2% CO_2.

Condition.	Period, hours.	Milligrams per 100 cc. of blood. Rob	Edw	Mos	Wes
Control drink in air	B	16.6	15.3	16.5	12.1
	1	17.2	17.5	21.9	12.6
	2	15.4	16.0	18.3	9.7
Control drink 10% O_2	B	17.3	....	....	13.4
	½	....	35.2	27.3	
	1	21.6	36.3	25.9	34.4*
	2	24.3	39.9	30.8	46.9
¾ gm. alcohol in air	B	....	14.3	10.2	9.7
	½	....	22.6	12.6	9.4
	1	30.1			
	2	24.9	19.2	18.3	29.9
¾ gm. alcohol in 50% O_2 and 2% CO_2	½	20.4	17.9	17.4	22.4
	1	19.2	14.4	14.6	
	2	15.3	13.4	16.1	12.1
1 gm. alcohol in air	B	....	....	10.4	16.7
	½	23.3	26.7		
	1	26.7	35.3	23.8	16.8
	2	28.6	34.2	26.5	28.5
1 gm. alcohol in 50° O_2 and 2% CO_2	B	14.2	16.2	12.1	17.5
	1	21.9	23.0	28.7	19.0
	2	28.1	19.0	18.3	20.6
1¼ gm. alcohol in air	½	26.4	41.8	26.7	28.9
	1	22.2	43.4	24.2	22.8
	2	31.0	40.9	42.3	24.6
1¼ gm. alcohol in 50% O_2 and 2% CO_2	½	30.7	35.1	24.0	26.2
	1	21.8	23.7	24.2	23.5
	2	24.6	20.7	23.1	24.7

PART III. In this part of the experiment 5 subjects, Wol, Mel, Fre, Ber, and Joh, were given the series of psychologic and physiologic tests after the ingestion of ¾ gm. of alcohol per kilo body weight. Blood samples were drawn ½, 1, and 2 hours following the ingestion of the alcohol.

In order to control the practice effects in the psychologic tests and also to check each blood alcohol series under similar conditions, each subject came without breakfast to the laboratory 11 times during a 3-month period. The experiments were given in the following order:

1. Control drink—air.
2. Control drink—50% oxygen.

3. Alcohol—50% oxygen and 2% carbon dioxid.
4. Alcohol—air.
5. Alcohol—50% oxygen plus 5% carbon dioxid.
6. Alcohol—50% oxygen plus 5% carbon dioxid.
7. Alcohol—air.
8. Alcohol—50% oxygen plus 2% carbon dioxid.
9. Alcohol—50% oxygen plus 0.2% carbon dioxid.
10. Control drink—50% oxygen.
11. Control drink—air.

TABLE 3.—LACTIC ACID DETERMINATIONS UNDER STRICTLY BASAL CONDITIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO ¾ GM. PER KILO BODY WEIGHT.

Condition.	Period, hours.	Milligrams per 100 cc. of blood.					
		Wes	Mos	Wal	Kne		Rob
Control drink in air . . .	B	8.2	9.5	16.2	10.4		9.6
	½	....	....	18.0			
	1	10.0	10.0	17.6	11.3		10.4
	2	8.9	9.2	15.6	10.7		11.3
Alcohol in air: I . . .	B	9.3	9.7	15.0	17.1		10.1
	½	....	....	....	21.8		
	1	16.8	12.3	23.8	21.8		11.8
	2	22.9	17.3	26.0	24.4		20.0
Alcohol in air: II . . .	B	....	....	16.7	12.8		
	1	....	....	22.5	15.7		
	2	....	....	20.6	15.5		
					A	B	
Alcohol, 50% O_2 and 2% CO_2: I	B	8.6	9.2	14.1	16.7	17.5	8.8
	1	11.3	11.5	12.3	16.5	22.0	10.9
	2	11.5	12.0	13.1	14.6	18.8	11.1
Alcohol, 50% O_2 and 2% CO_2: II	B	....	....	14.9	9.8		
	1	....	....	19.6	9.6		
	2	....	....	18.4	8.1		

Table 4 and Fig. 1 shows the grams of alcohol per 100 cc. of blood under the various conditions as indicated. If one compares the concentration of alcohol in the blood while breathing air with the series while breathing concentrations of 50% oxygen plus 0.2 to 5% carbon dioxid, it is apparent that the oxygen and carbon dioxid had the effect of lowering the alcohol concentrations. These differences are statistically significant.

After the ingestion of alcohol in air there was an initial increase in the pulse rate followed by a fall. If a similar alcohol drink was taken while breathing concentrations of 50% oxygen and 5% carbon dioxid, then there was a noticeable increase in the pulse rate as well as in the variability which was associated with the increased pulmonary ventilation due to the excess carbon dioxid. If the alcohol was taken while breathing 50% oxygen and 2% carbon dioxid, the rate and variability of the pulse was diminished as compared to a similar alcohol drink in air. There was a tendency

for the pulse rate to be slowed in the control series with no alcohol and 50% oxygen in the inspired air.

TABLE 4.—BLOOD ALCOHOL DETERMINATIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO ¾ GM. PER KILO BODY WEIGHT.

Condition.	Period, hours.	Grams per 100 cc. of blood.				
		Wol	Mel	Fre	Ber	John
Alcohol in air: I	½	.056	.066	.131	.084	.114
	1	.109	.190	.104	.084	
	2	.090	.102	.177	.069	.065
Alcohol in 50% O_2 and 2% CO_2: I	½	.043	.018	.043	.032	.059
	1	.048	.017	.058	.054	.052
	2	.058	.035	.052	.051	.040
Alcohol in 50% and 5% CO_2	½	.073	.030	.085	.046	.068
	1	.101	.048	.083	.058	
	2	.108	.063	.077	.079	.069
Alcohol in 50% and 5% CO_2: II	1	.054	.121	.089	.068	
	2	.089	.106	.074	.082	
Alcohol in air: II	½	....	.068			
	1	.058	.084	.082	.059	
	2	.102	.092	.164	.082	
Alcohol in 50% O_2 and 2% CO_2: II	1	.085	.118	.087	.094	
	2	.080	.090	.094	.095	
Alcohol in 50% O_2 and 0.2% CO_2: I	½	.090	.050	.092	.074	.060
	1	.099	.059	.090	.073	.065
	2	.100	.059	.061	.050	.059

PART IV. Fourteen subjects were given an alcohol drink corresponding to ¾ gm. per kilo body weight diluted with water and orange juice to equal a total volume of approximately 250 cc. Each subject came to the laboratory twice and was tested once in air and once on 50% oxygen and 2% carbon dioxid. Twenty cc. of venous blood was taken ½, 1, and 2 hours after the ingestion of the alcohol. The results are given in Table 5. The procedure was slightly different in the case of Kne, Sor, Eck and Fel in that they took the series of psychologic tests mentioned above. All of the other subjects reclined on the bed throughout the 2-hour period. The averages of the blood alcohol determinations in air as compared with high oxygen gave statistically reliable differences for this group of 14 subjects. The differences were not reliable for individuals Eck, Sch, Cum, Dem, and Har. In the case of Sor, Wal and Art whose basal rates were below −20 the differences were very marked.

In order to determine the effects of 50% oxygen plus 2% carbon dioxid as compared to air, on the concentration of alcohol in the blood, the average for 23 subjects for the alcohol drink consisting of ¾ gm. per kilo body weight was computed. The averages for 50% oxygen and air were compared at ½, 1, and 2 hours and treated by Fisher's method[27] for the reliability of the observed difference. The results indicate that ½ hour after the ingestion

of alcohol the chances are 70 to 80 in 100 that the observed difference is reliable, *i. e.*, that the excess oxygen had a beneficial effect. At the end of the 1-hour and 2-hour periods, the chances are 99 in 100 that the decrease in blood alcohol in the high oxygen and carbon dioxid is reliable.

TABLE 5.—BLOOD ALCOHOL DETERMINATIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO ¾ GM. PER KILO BODY WEIGHT IN AIR, AND IN 50% O_2 AND 2% CO_2.

Condition.	Period, hours.	Grams per 100 cc. of blood.														
		Kne Series I.	Kne Series II.	Sor.	Eck.	Yan.	Fel.	Sch.	Wal.	Cum.	Art.	Max.	Ben.	Dem.	Har.	Nat.
Alcohol in air	Before*	...	...	...	...	.011	...	...	.013	...	...	.014	.012	.014		
	½	.020	...	.066	.034	...	.036	.050	...	.082	.016					
	1	.050	.055	.105	.057	.073	.057	.079	.131	.074	.073	.060	.054	.046	.078	.063
	2	.088	.076	.083	.106	.064	.067	.074	.147	.063	.085	.069	.059	.053	.073	.047
Alcohol in 50% O_2 and 2% CO_2	Before*	...	...	...	...	.013	...	...	.012	...	...	...	.012	.014		
	½	.061	...	.054	.046	...	.041	.046	...	.053	.065	.039	.041	.083	.080	.036
	1	.075	.037	.064	.178	.030	.050	.074	.039	.072	.072	.069	.057	.073	.078	.038
	2	.055	.051	.035	.103	.051	.039	.075	.059	.077	.057	.052	.034	.057	.069	.024

* Amount of alcohol in the blood previous to the ingestion of the alcohol drink.

Psychological Tests. In Table 6 the average responses are shown for the 14 subjects who took the psychologic tests in air and in high oxygen following the alcohol drinks of ¾ gm. per kilo body weight. In general the reaction of each subject after the alcohol drink was better with the 50% oxygen and 2% carbon dioxid than in air. In treating the data for the statistical reliability of the observed difference by Fisher's Method, it was found that the differences were reliable with the exception of the Choice Reaction and Digit Symbol tests in which cases the chances were only 40 to 50 and 60 to 70 in 100 that the high oxygen had a significantly beneficial effect. The improvement in individual cases was very striking. In several of the subjects, however, where the blood alcohol determinations were not significantly different in air and in high oxygen the psychologic tests likewise showed only slight differences if any, for example, Eck and Kne.

The average individual response for each of the 14 subjects in the 6 tests shows a general tendency toward improvement after the ingestion of alcohol in high oxygen as compared to air. Out of 84 chances to perform, improvement occurred in 63 cases (75%); 12 (14%) cases were slightly worse and in 9 (10.5%) there was no significant change.

In comparing the variability of response following the ingestion of alcohol in air and in 50% oxygen with the control series without alcohol, there is an increase in the standard deviation in all tests with the exception of Dotting. After the ingestion of alcohol in high oxygen the average responses were less variable as compared to alcohol in

air. This was especially noticeable in the Choice Reaction, Color Naming and Code tests. In each of these tests the standard deviation is approximately twice as large in air as in high oxygen (Table 6).

TABLE 6.—RESULTS OF PSYCHOLOGICAL TESTS FOR 14 SUBJECTS IN AIR, AND IN 50% O_2 AND 2% CO_2 AFTER INGESTING DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO $\frac{3}{4}$ GM. PER KILO BODY WEIGHT.

	Control air.		Control 50% O_2.		Alcohol and 50% O_2.		Alcohol air.	
	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.
Choice reactions	34.4	2.3	35.8	2.9	36.0	3.9	38.6	6.5
Color naming	48.1	5.9	47.4	7.3	52.4	8.5	61.1	17.5
Pursuit meter	37.9	5.4	35.0	6.2	40.5	10.2	43.9	11.0
Dotting	17.6	2.5	18.1	2.8	17.9	2.4	14.9	2.5
Digit symbol	164.5	24.3	170.3	25.6	157.3	26.8	139.6	29.6
Code test	118.1	12.3	119.7	11.0	122.1	15.2	137.3	27.0

Summary. In this study 23 subjects under various degrees of alcoholic intoxication were tested in an oxygen chamber to determine the value of 50% O_2 and from 0.2 to 10% CO_2 in counteracting the effect of the alcohol. The drinks varied from $\frac{3}{4}$ to $1\frac{1}{4}$ gm. of ethyl alcohol per kilo body weight diluted to a total volume of about 250 cc. or $\frac{1}{3}$ alcohol and $\frac{2}{3}$ water and orange juice. In order to determine the efficacy of the excess oxygen and carbon dioxid in counteracting the effect of the alcohol samples of venous blood were drawn $\frac{1}{2}$ hour, 1 and 2 hours following the drink and analyzed for blood alcohol and lactic acid. The alterations in behavior were studied by a series of 6 psychological tests. The respiration, pulse and blood pressure was taken at regular intervals. Control experiments were run in air and low oxygen with and without alcohol. The results were as follows:

1. The amount of alcohol in the venous blood showed a tendency to decrease while breathing 50% oxygen and excess carbon dioxid as compared to air. In a number of cases the decrease was more than 50%. In 5 of the 23 subjects, however, the decrease was not significant.

2. An increase in the lactic acid of venous blood was observed following the ingestion of alcohol in air. This increase was not as great when the subjects breathed 50% oxygen and excess carbon dioxid. The observed differences were statistically reliable for the group, especially when the subjects reclined throughout the 2-hour period.

3. After the ingestion of the alcohol in air the pulse and blood pressure on the average showed a transient rise followed by a return to the normal or subnormal rate. Following the larger doses there was a fall in the blood pressure and the pulse became smaller in volume. Following the alcohol drinks in 50% oxygen the variations in pulse and blood pressure were not so great. The changes in rate of respiration were not significant. In a few cases, however, the larger amounts of alcohol in air tended to decrease the rate of respiration.

4. There was a general tendency toward improvement in the 6 psychologic tests after the ingestion of alcohol in high oxygen and excess carbon dioxid as compared to air. The variability of reaction also decreased in high oxygen. The average differences for the group of 14 subjects were statistically reliable in the Code, Dötting, Color Naming and Pursuit Meter tests. For the 14 subjects in the 6 tests there was an increase in efficiency while breathing excess oxygen and carbon dioxid in 63 out of 84 possible chances or in 75% of the tests.

Conclusion. The inhalation of 50% oxygen with an increased percentage of carbon dioxid for 2 hours lowered the alcohol and lactic acid contents of venous blood in subjects who had previously ingested from $\frac{3}{4}$ to $1\frac{1}{4}$ gm. alcohol per kilo body weight; this was accompanied by a corresponding improvement in mental and motor behavior. In certain individuals, however, or in about 20% of the subjects tested, these changes did not occur. There is no evidence whether this was due to differences in basal metabolism, general physiological condition or certain physiological idiosyncrasies in rate of oxidation.

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FURTHER STUDIES ON AZOTEMIA FOLLOWING HEMORRHAGE IN THE DIGESTIVE TRACT.

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It has long been well known that increased blood-urea values may be observed in several pathologic conditions besides renal affections. This concerns principally obstruction of the intestinal tract combined with vomiting, certain infectious diseases, especially pneumonia, starvation, deprivation of water, shock and various postoperative conditions.

Even now the explanation of this azotemia, evidently often accompanied by hypochloremia, can hardly be said to be quite satisfactory. Blum[1] has conceived the idea of "l'azotémie par manque de sel," the hypochloremia being to him of primary importance, the azotemia only serving the maintenance of osmotic equilibrium. Still, this theory is hardly tenable, for one thing because of the difference in diffusion power between chlorids and urea.

Frequently an increased toxic destruction of proteins is assumed to cause azotemia; in other cases the dehydration of the tissues is believed to be the cause. It is assumable, however, that the latter causes hypochloremia and a reduced excretion of chlorids, but still the existence of a consecutive relation between chlorids and urea of the blood has not been definitely proved, the frequent simultaneous occurrence of the two conditions, azotemia and hypochloremia, being no proof. On the contrary, the investigations of Courriades[4] with experimentally hypochloremic dogs prove that hypochloremia is not necessarily accompanied by azotemia.

In addition to the above-mentioned conditions, increase of blood-urea values may be observed in anemia subsequent to repeated severe hemorrhages, as shown by Taylor and Lewis;[11] these authors, however, perfectly well understood that anemia itself did not cause the increased values, the increase lasting but a few days and disappearing a long time before the red blood cell counts became normal again. The increase was supposed to be caused by the sudden reduction of the volume of the blood.

Concerning the influence of hemorrhage in the digestive tract on the blood urea, but few observations can be traced. Sanguinetti,[8] in 9 cases of hemorrhage from ulcers in the stomach and the duodenum observed increased blood-urea values, these being caused, he assumes, partly by an increased destruction of proteins in the body, partly by the resorption of the large quantities of blood accumulated in the intestines. In accordance with this view he succeeds in a few experimental cases in observing increased blood-urea values subsequent to oral administration of blood in normal

persons. In 1935 Clausen[3] communicated a similar observation. In Denmark, Christiansen[2] has recorded 2 cases of severe hemorrhage from gastric ulcers; in both cases considerable increase of blood-urea values was observed together with the cessation or reduction of chlorid excretion in urine. The explanation indicated is the resorption of toxic substances originating from the blood accumulated in the intestinal tract, combined with a diminished supply of chlorids in the food.

Apart from these few observations, all of them made in recent years, no other case of azotemia subsequent to hemorrhage from the digestive tract seems to be recorded. It, therefore, seemed desirable to investigate whether this azotemia appears regularly in hematemesis and melena, or is it a phenomenon observed only in hemorrhages having a violent and perhaps lethal course? Furthermore, I have attempted to study the various circumstances that are supposed to be favorable to the development of azotemia, as no tenable theory, judging from the reports referred to, has been made as yet concerning the origin of azotemia.

Part of this work was reported at the XVII Scandinavian Congress of Internal Medicine, the rest having been made since; but, as all the investigations form a unity, they will here be published in full.

Method. The investigations have been carried out upon 26 patients admitted during the months of March to September, 1935 to the Medical Departments B and C of Bispebjerg Hospital, Copenhagen, suffering from hematemesis and melena. Eighteen of the patients were mentioned in the report at the Congress; 23 were admitted to Department B, only 3 being treated at Department C. The hemorrhage in 22 cases undoubtedly originated from gastric or duodenal ulcers; in 2 cases the cause of the hemorrhage was suspected to be esophageal varices, and this turned out to be evident in a 3d case, as shall be shown later. Finally in 1 case the possibility of cancer could not be disregarded. All patients admitted to Department B were treated in the same way, in accordance with the principles indicated by Meulengracht,[7] viz.: plenty of food in the form of a full purée diet, ferrous lactate and pulvis alkalinus from the very first day of their admission. The 3 patients treated in Department C during the first 24 hours after their admission received only ice-water and coagulen; later they were treated with a rather quickly progressing ulcer diet, individually varying somewhat in the increases.

One of the 26 patients who died will be mentioned separately later. The highest values of blood urea in the remaining 25 patients appear in Table 1:

TABLE 1.—HIGHEST VALUES OF BLOOD UREA.

Blood urea in mg.%	Cases
Above 70	1
60 to 69	4
50 to 59	7
39 to 49	9
Below 39	4
Altogether	25

From Table 1 it appears that a blood-urea value of 50 mg.% and above, which according to McKay and McKay[6] must be regarded as absolutely increased, was observed in 12 of the 25 patients; 9 showed a highest value between 39 and 50 mg.%; in 4 patients only, no increase of blood urea above 39 mg.% was observed. It is thus obvious that about half of these patients suffering from hematemesis and melena presented blood-urea values that were absolutely above the normal. It is furthermore evident that in 9 patients values were observed exceeding the limit indicated by McKay and McKay as the general normal highest value: 38 mg.%.

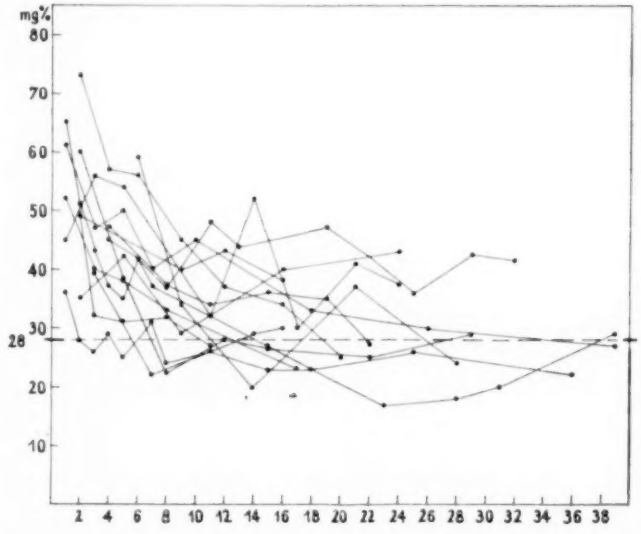

FIG. 1.—Blood urea values in 15 patients; the abscissa indicates days after first observation of hemorrhage.

The observed increase appears more distinctly from Figs. 1 and 2 than in the table. In Fig. 1 the blood-urea values of the 15 patients first observed are plotted graphically, the abscissa indicating in days the time expired since hematemesis or melena was first observed, the ordinate indicating blood urea in mg.%. In Fig. 2 a curve is plotted indicating the average values from the same 15 patients. Fig. 2 shows that the day after the hemorrhage was first observed in these patients an average increase of blood urea up to 52 mg.% was found. Furthermore, it is evident that this azotemia was considerably reduced during the first days, then continuing slightly increased, to return in the course of 3 to 4 weeks to the value regarded as normal according to McKay and McKay, 28 mg.%.

The azotemia has shown no relation to the severity of the anemia, as distinctly appears in Fig. 3; in this figure the abscissa indicates

the hemoglobin percentage, while the ordinate indicates blood urea in mg.%. From the figures representing the 25 patients and corresponding to the highest blood-urea value observed in each patient

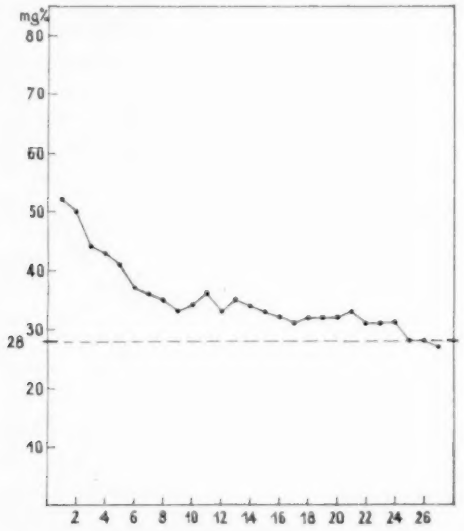

FIG. 2.—Average blood urea values of the above 15 cases.

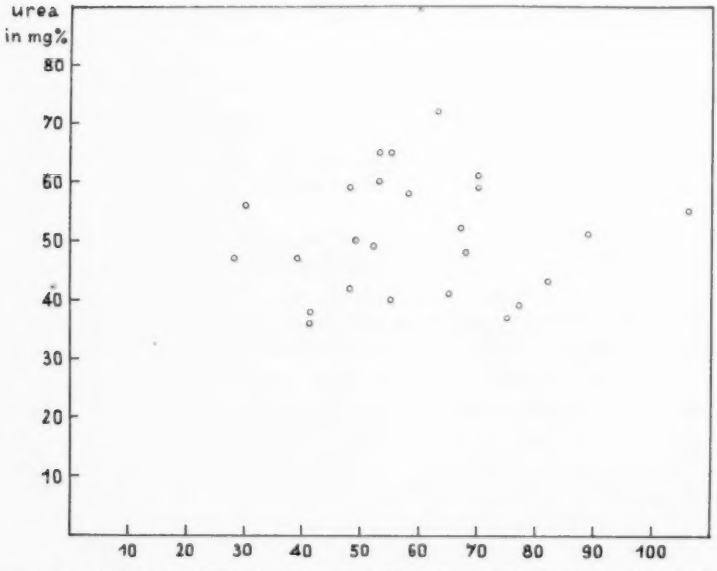

FIG. 3.—Highest values of blood urea in 25 patients and coëxistent hemoglobin percentages.

it is seen that any combination between blood-urea values and hemoglobin percentage may occur; thus increased blood-urea values

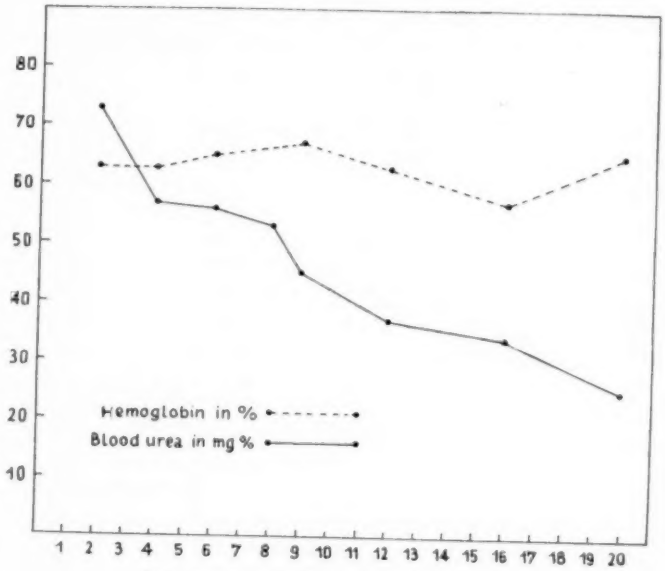

FIG. 4.—Case T. E. J. G., male, aged 42.

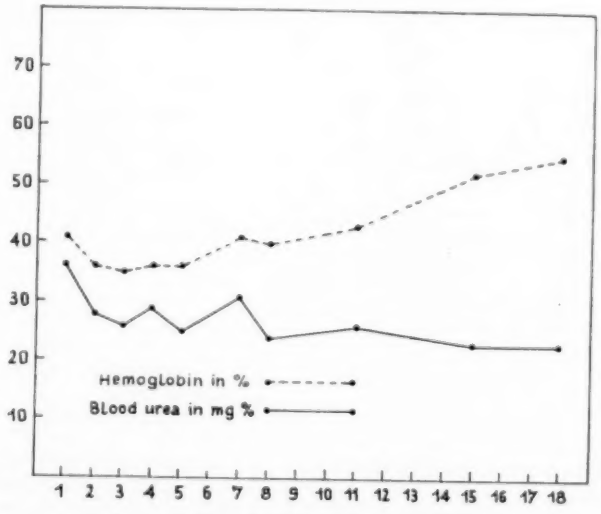

FIG. 5.—Case D. F. G., female, aged 29.

frequently are observed together with normal, or moderately lowered hemoglobin percentage, as shown in Fig. 4. On the other hand,

normal blood-urea values are sometimes found in rather pronounced anemia, as is apparent from Fig. 5.

In contradistinction to the mortality of ulcer hemorrhages, as shown by Meulengracht,[7] and the regeneration of the blood, as indicated by Schiödt,[9] both of which have turned out to be excessively dependent on and influenced by the treatment with abundant nutrition, the azotemia has shown no relation to the different methods of treatment. It is true that, as stated, I have only 3 cases treated with ulcer diet, but in these cases the azotemia hardly developed more than in those treated with plenty of food, just as the further course of the azotemia seems to be parallel in all cases.

Only 2 of the 25 patients have been very exhausted, 1 being admitted in a shocked condition, the other gradually bleeding down to a hemoglobin percentage of 21 and 870,000 red blood cells; in both the blood urea was found to be increased up to 73 and 56 mg.%, respectively; against this the remaining 10 patients in whom blood urea exceeded 50 mg.% felt relatively well. Thus no closer relation seems to exist between the extent of the increase and the condition of the patients, at least not within the observed limits.

These observations seem to have established the presence of an increased blood urea; if not very great, at any rate almost invariably, during the first days after hemorrhages in the digestive tract. The cause of it can scarcely be explained with absolute certainty, but the circumstances connected with one of the patients might give a hint:

The patient, a man, aged 53, was admitted June 7, 1934 into Department B suffering from hematemesis and melena. Eight days previously he first observed melena, with daily recurrence. At the time of admission, after having had 2 severe hemorrhages he was extremely exhausted, and during the following days he had several copious tar-colored stools together with frequent vomitings, all of the latter containing large quantities of fresh blood. Because of the vomiting he retained little of the purée diet with abundant fluid prescribed as usual, and, in spite of two transfusions of blood, he steadily grew worse, making a restless uremic impression; he died on the 10th of June, having during the last day and night been almost comatose.

Autopsy revealed about 400 cc. of blood in the stomach, the hemorrhage originating from a burst esophageal varix. A cirrhosis of the liver was also found, together with multiple small abscesses in the liver, both of which were assumed to have contributed to the development of the varices. Microscopic examination of the kidneys showed slight arteriosclerotic changes, otherwise nothing abnormal. The various examinations appear in Table 2.

From Table 2 the rise in blood urea is apparent. The decreased urea excretion was caused both by the reduced diuresis and by the reduction of urea concentration in urine. The chlorids in the urine, already reduced to about half of the normal value, the next day only amounted to 1/20 of the normal value. The heavy reduction of urea excretion might be suggestive of a reduced renal function, and accordingly the urea clearance was determined, the first day giving 80% of the normal value, the following day only 15% of the normal. During the last 2 days the various examinations could not be made, the patient being very restless and urinating involuntarily; the last day anuria practically set in.

TABLE 2.—DATA ON CASE, M. P., MALE, AGED 53.

Date:	6/7.	6/8.	6/9.	6/10.
Days after first hemorrhage	8	9	10	11
Hemoglobin percentage	50	44		
Red blood cells, in millions	2.48			
Diuresis in cc.	555	330	ca100	0
Urea in 24 hours' urine in mg.%	2580	580		
Excreted urea in grams	14.3	1.91		
Cl in 24 hours' urine (as NaCl) in mg.%	525	66		
Excreted Cl (as NaCl) in grams	2.61	0.22		
Blood urea in mg.%	51	97	148	216
Urea clearance in %	80	15		
Blood pressure in mm. Hg.	....	75/60	60/40	

According to these observations it seems permissible to explain the increase of blood urea together with the clinical symptoms of uremia as being caused by the reduction of the renal function. According to Van Slyke and coworkers,[12] the clinical symptoms of uremia set in when the urea clearance is reduced to 5% of the normal. This agrees fairly well with the morbid process in this patient, his uremic condition not beginning until the third day, the urea clearance at that time being most likely considerably below the 15% of the preceding day.

Now what causes the reduction of and finally the total cessation of the renal functional? As stated, no evidence was found microscopically of any organic renal affection of importance, and no pathologic elements were found in the urine. There must have been thus a functional reduction of the renal function. As is seen from the table, however, the blood pressure was lowered to about the point where a considerable diminution of filtration in the glomeruli sets in, according to Lassen.[5] Therefore, the possibility cannot be dismissed that here the lowered blood pressure by means of greatly reduced filtration has caused the observed reduction of renal function. This caused the azotemia and was contributory to, if not directly causing, death. It is conceivable that a possible resorption of toxic substances from the intestinal tract and a dehydration of the tissues may also have had some bearing on the development of azotemia; the practical cessation of the excretion of chlorid suggests the existence of such processes. It cannot now be decided whether a possible injury of the liver may have been contributory, but it may be recollected that in pathologic conditions with an injured liver, *e. g.*, acute yellow atrophy of the liver, lowered blood-urea values are generally found, indicating a diminished capacity of urea formation in the liver (Stadie and Van Slyke[10]).

According to the aforesaid observations, however, severe azotemia as just described does not develop in the usual case of hematemesis and melena. The question is, then, if the increase of blood urea generally observed is produceable in a manner similar to that in the case described. In order to get this question answered if pos-

sible I have studied the renal function in 4 other patients. The first was admitted 1 day after a small hematemesis. The results appear in Table 3:

TABLE 3.—DATA OF CASE, C. J., MALE, AGED 55.

Date:	6/10.	6/11.	6/12.	6/13.	6/14.	6/15.	6/16.	6/17.	6/18.
Days after hemorrhage	1	2	3	4	5	6	7	8	9
Hemoglobin percentage	.....	89	.....	.....	80	.....	.....	87	
Red blood cells, millions	.....	4.45	.....	.....	4.90	.....	.....	4.02	
Diuresis in cc.	500	1485	930	1970	1450	1580	750	1200	915
Urea in 24 hours' urine mg.%	1640	1260	1300	1140	1060	.....	1460	2600	1460
Excreted urea in grams	8.20	18.71	12.09	22.46	15.37	.....	10.95	31.20	13.36
Cl in 24 hours' urine mg.%	107	170	232	482	627	794	648	398	419
Excreted Cl in grams	0.54	2.53	2.16	9.50	9.09	12.35	4.86	4.78	3.83
Blood urea in mg.%	.....	51	43	37	35	42	.....	37	34
Urea clearance in %	.....	73	37	190	90	133	.....	121	158

N.B.—The figures in the first column refer to 12 hours only.

Table 3 shows that though it was a case of hematemesis not exercising any influence on the hemoglobin percentage, blood urea was found to be increased to 51 mg.% together with a reduced chlorid excretion. Urea clearance is a little lowered in the first two determinations, whereafter it is about or above the normal limit. It must, furthermore, be noticed that the blood pressure was quite normal all the time.

The second patient was admitted 4 days after melena was first observed.

TABLE 4.—DATA OF CASE, E. V., FEMALE, AGED 25.

Date:	6/13	6/14	6/15	6/16	6/17	6/18	6/19
Days after hemorrhage	4	5	6	7	8	9	10
Hemoglobin percentage	.....	48	.....	.....	.....	.....	43
Red blood cells in millions	.....	2.615	.....	.....	.....	.....	2.815
Diuresis in cc.	1075	680	875	1420	800	1245	1370
Urea in 24 hours' urine in mg.%	3500	3420	....	1340	1300	980	720
Excreted urea in grams	37.63	23.26	....	18.93	10.40	12.20	9.86
Cl in 24 hours' urine in mg.%	398	544	....	440	1198	378	294
Excreted Cl in grams	4.28	3.70	....	6.25	9.34	4.71	4.03
Blood urea in mg.%	.....	42	30	.....	26	49	27
Urea clearance in %	.....	135	157	.....	117	72	138

N.B.—The figures in the first column refer to 17 hours only.

From Table 4 it appears that blood urea during the first days is only slightly increased, while chlorid excretion is a little lowered, but quickly becomes normal. At the same time a rather considerable urea excretion takes place. Urea clearance is above the normal. On the evening of June 17 the patient felt weak and ill, having epigastric oppression, and next morning blood urea had risen to 49 mg.%, chlorid excretion had fallen to one-third, and urea clearance, which all the time had been about normal value, had fallen to 72%. The following day matters were normal again, except that the chlorid excretion was still somewhat reduced. The blood pressure was normal all the time, but unfortunately was not examined at the time of the slight indisposition.

The third patient was admitted 8 days after the first observation of melena.

From Table 5 it is apparent that, although blood urea in the days immediately after admission was moderately increased, urea clear-

ance was still quite normal. In this case, as in the 2 cases previously reported, the increase of blood urea seems to be of very short duration. And here again the blood pressure was found to be normal at all examinations.

TABLE 5.—DATA OF CASE, V. L., MALE, AGED 51.

Date:	6/20.	6/21.	6/22.	6/25.
Days after hemorrhage	8	9	10	13
Hemoglobin percentage	.....	48	.....	45
Red blood cells in millions	.....	2.39	.....	1.97
Diuresis in cc.	650	700	700	
Urea in 24 hours' urine in mg.%	3200	2620	2340	
Excreted urea in grams	20.80	18.34	17.38	
Cl in 24 hours' urine in mg.%	357	544	336	
Excreted Cl in grams	2.32	3.81	2.35	
Blood urea in mg.%	.....	59	39	33
Urea clearance in %	.....	98	131	

NB.—The figures in the first column refer to 12 hours only.

Of a fourth patient, admitted because of several hematemeses during 2 preceding days, it may briefly be stated that, in spite of a hemoglobin percentage of 58 and a blood urea of 58 mg.% at the time of admission, his urea clearance was found to be quite normal in the following days; nor did his blood pressure at any time show anything abnormal.

From these latter observations it seems that the relation between the renal function and azotemia, undoubtedly found in severe cases of intraintestinal hemorrhage, cannot be observed in the slighter cases, which in all cases examined exhibited a normal renal function and an unimpaired capacity for urea concentraction. The transitory reduction of urea clearance mentioned in Table 4 thus seems to be of no importance. Consequently the azotemia in these slighter cases must be explained in some other way, such as by the intestinal resorption and dehydration causing toxic destruction of proteins.

In the severe cases, however, the functionally reduced renal function caused by lowered blood pressure seems to be of decisive importance in the development of azotemia, resorption and dehydration alone scarcely being able to cause an increase of blood urea as great as that described.

Summary. It is demonstrated that for days after hemorrhage in the digestive tract increased blood-urea values are generally observed. Of 26 patients suffering from hematemesis and melena, absolutely increased values (*i. e.*, above 50 mg. %) were found in 13, while in 9 other patients values between 39 and 50 mg. % were observed; in 4 patients only no increase above 38 mg. % was found.

In 1 of the patients blood urea was found to be increased up to 216 mg. %, and he died 4 days after admission, with uremic symptoms, without any apparent organic renal affection. At the same time, however, there was a heavy reduction of urea clearance and a very low blood pressure; for this reason the theory is advanced, that the

observed increased blood urea at least partly is due to a functional reduction of the renal function, caused by the low blood pressure.

In order to investigate whether the increase of blood urea found in the slighter cases of intraintestinal hemorrhage might have been due to a similar mechanism, the renal function was determined in 4 patients suffering from hematemesis and melena, but in these cases no reduction was found. It is therefore assumable that the increase of blood urea in these cases is caused by resorption of blood in the intestine and by dehydration of the tissues.

Since the completion of this paper two others, dealing with the same subject have appeared, Sučić, D.: Akute Azotämie bei grossen gastro-intestinalen Blutungen, Klin. Wchnschr., **14**, 1316, 1935; Ingegno, A. P.: The Elevated Blood Urea of Acute Gastro-intestinal Hemorrhage and Its Significance, Am. J. Med. Sci., **190**, 770, 1935.

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THE EXCRETION OF FERROCYANID IN MAN IN RELATION TO THE UREA CLEARANCE.

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It is desirable in the study of renal function that at least one method be available which bears a direct relation to the amount of glomerular filtration. Stieglitz and Knight,[1] with this in mind, have proposed that the rate of excretion of sodium ferrocyanid be used

as an index of renal function. They found that following the intravenous administration of about 0.25 gm. of anhydrous sodium ferrocyanid normal individuals excreted 11 to 25% in 1 hour, 20 to 38% in 2, and 26 to 52% in 3 hours. Patients with known renal insufficiency excreted traces or none. In a group of hypertensive patients the excretion was considerably less than in the normal group. The patients with hypertension had little impairment of renal function as measured by the 2-hour phenol red excretion, although somewhat more impairment is deduced from their graphs of the phenol red excretions in shorter periods. The authors felt that the patients in the hypertensive series had diminished renal function, particularly as regards efficiency of glomerular filtration.

The present report is concerned with additional evidence relating to the ferrocyanid test, with particular regard to a comparison of ferrocyanid excretions with urea clearance levels.

Material. The subjects were selected for the test to provide as wide a range of urea clearance levels as possible, rather than on the basis of the type of disease present. Of the 102 tests on which most of the discussion is based, 19 were in subjects free from renal or vascular disease, 23 were in patients in various stages of glomerulonephritis, and 60 were in patients with arteriosclerotic Bright's disease, chiefly primary hypertension. Several of the last group had myocardial insufficiency.

Method. The tests were carried out in the morning. Breakfast was omitted and water was administered freely enough that in most instances a maximum clearance,[2] *i. e.*, a urinary output of 2 cc. a minute or more, was obtained. The subject voided and the time was noted. Within a few minutes 0.5 gm. of hydrated sodium ferrocyanid,* equivalent to 0.27 to 0.29 gm. of the dry salt, was administered intravenously in 10 cc. water, and the time was noted. Urine was collected after 1, 2, and 3 hours, and blood was withdrawn for urea determination after 1 hour. A large aliquot of each of the urine specimens was titrated for ferrocyanid by the copper sulphate method described by Stieglitz and Knight.[1] The ferrocyanid excretion was expressed in per cent of the content of one ampule; titration of a few ampules from each batch was necessary to provide the standard. The urea concentrations of the blood and urine were determined gasometrically[3] and the urea clearance was calculated for each of the first two collection periods. Clearances were corrected for height[4] and expressed as per cent of normal, 54 cc. a minute being regarded as 100% for standard and 75 cc. as 100% for maximum clearances.

In dealing with urines containing more than traces of blood the method was altered somewhat from that advised by Stieglitz and Knight. When known amounts of ferrocyanid are added to urine containing blood and protein and the protein is precipitated by boiling there is a varying loss of ferrocyanid from the filtrate. Recovery of known amounts of ferrocyanid within 4% was obtained if the urine was refrigerated promptly and centrifuged within a few hours of voiding, and if aliquots of the supernatant urine were titrated while cold. This procedure was followed, therefore, in patients with hematuria. At times there had been enough hemolysis that the endpoint could not be obtained and the test had to be discarded.

Toxicity. Undesirable reactions were few and never serious. In 3 of 122 tests there was nausea for less than 30 seconds after the cessation of the

* Sterile sodium ferrocyanid was furnished in ampules through the courtesy of the Abbott Laboratories.

injection. This may have been due to undue speed in administration. Four men, 3 with mild symptoms of prostatic obstruction, complained of dysuria, urgency and frequency lasting several hours. In one instance there was complete inability to void for 14 hours. More recently administration of ferrocyanid has been avoided in patients with symptoms of prostatism.

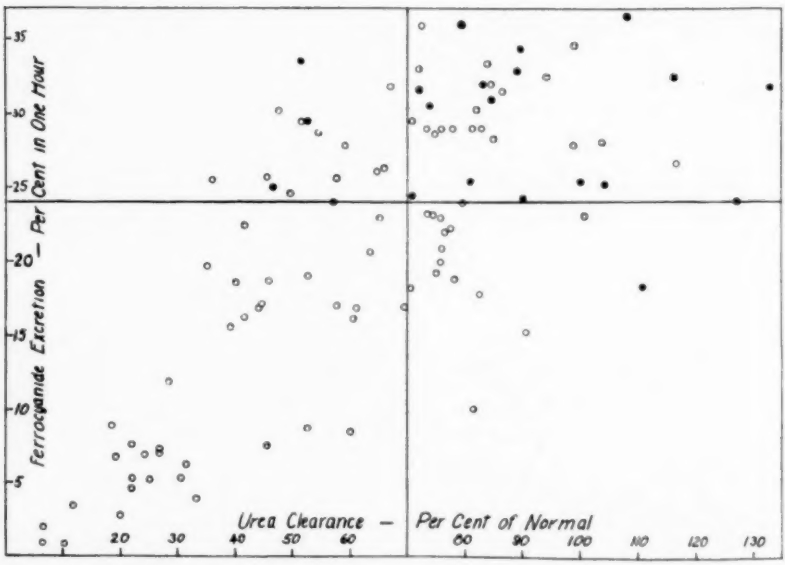

FIG. 1.—Mean clearance and 1-hour ferrocyanid excretion in 102 tests. Solid dots represent normal subjects.

RESULTS. Figure 1 shows the distribution of various levels of ferrocyanid excretion in 1 hour with reference to the mean level of urea clearance. A line is drawn at 70% clearance, which may be regarded in general as a lower limit of normal function, although occasional subjects who are apparently well at times have clearances below this figure. Another line is drawn to correspond with a ferrocyanid excretion of 24% for purposes of further comparison. Graphs of the 2 and 3-hour excretions in comparison with the mean clearances do not differ in any essential from the graph of the 1-hour excretion. The distribution of various ferrocyanid excretion levels with reference to urea clearance is tabulated in Table 1.

Excretion of ferrocyanid in normal subjects generally exceeded 24% in 1 hour, 35% in 2, and 50% in 3 hours (Fig. 1, Table 1). These levels were reached by a considerable number with moderately diminished (30 to 70% of normal) clearance as well. The urea clearance indicates impairment of renal function as a rule in those subjects who excrete less than 18% in 1 hour, 30% in 2, and 40% in 3 hours. Those in whom the ferrocyanid excretion exceeded 18% in 1 hour and failed to reach 24% were predominantly hypertensive patients with moderately diminished or low normal urea clearances.

TABLE 1.—FREQUENCY OF VARIOUS FERROCYANID EXCRETIONS IN PATIENTS CLASSIFIED ACCORDING TO MEAN UREA CLEARANCE.

	Urea clearance less than 30%.	Urea clearance 30% to 70%	Urea clearance 70% or more.
Total number 1-hour tests	15	36	51
Number in which ferrocyanid excretion was above 15%	0	30	50
Above 18%	0	22	48
Above 24%	0	15	36
Total number 2-hour tests	15	36	51
Number in which ferrocyanid excretion was above 20%	1	32	51
Above 30%	1	23	47
Above 35%	0	20	42
Total number 3-hour tests	12	33	51
Number in which ferrocyanid excretion was above 30%	1	28	51
Above 40%	0	22	49
Above 50%	0	12	38

Those subjects who excreted more than 24% of ferrocyanid in 1 hour and whose clearances were above 70% of normal were normal subjects or hypertensive patients without signs of renal impairment. Those in whom the tests were concordantly low uniformly had glomerulonephritis, advanced hypertension, or advanced arteriosclerosis. The subjects in whom the results of the tests were discordant are listed in Table 2, with additional data. The majority of these were patients with glomerulonephritis or hypertension, although 4 apparently normal individuals were included.

Subjects of 32 tests had urea clearances without injection of ferrocyanid within a few days of the combined test, or, in a few instances, during the hour preceding the injection of ferrocyanid. The clearance levels were higher with the combined test in 17 and lower in 15; in no case were variations of significant degree.

In Figure 2 are represented 1-hour ferrocyanid excretion and mean urea clearance in subjects in whom there were repeated tests. The agreement of the two tests is apparently no greater in a single individual at different times than in the series as a whole.

In order to choose the optimal time of measuring ferrocyanid excretion the mean urea clearance for the 2 hours was correlated with excretion in 1, 2, and 3 hours respectively by the Pearson product-moment formula.[5] A correlation of about 0.7 was found in each instance (Table 3). Because of the fact that there are differences in the clearance from 1 hour to another, a comparison was also made of the first hour ferrocyanid excretion with the clearance during that hour. The correlation was increased slightly, not significantly, above that with the mean clearance for the period. It being theoretically possible that the second hour excretion might be a more stable measure than the first, the second hour excretion was calculated for each individual as a fraction of the ferrocyanid remaining

in the body at the end of the first hour. These quantities correlated much less with the clearance than did the cumulative totals and are probably of no clinical value.

TABLE 2.—DATA ON SUBJECTS IN WHOM THE TESTS WERE DISCORDANT.

	Ferrocyanid above 24% in 1 hour, clearance below 70% of normal.		Ferrocyanid below 24% in 1 hour, clearance above 70% of normal.	
	Age.	Remarks.	Age.	Remarks.
1. Discrepancy slight	28	Acute glomerulonephritis	53	Hypertension known 4 yr.; albumin and casts in urine intermittently.
	52	Hypertension known 15 years, traces of albumin in urine intermittently	59	Peripheral arteriosclerosis, systolic hypertension; normal urine.
	58	Hypertension of uncertain duration, no albumin	67	Hypertension known 3 yr.; occasional erythrocytes in urine, no albumin.
			54	Hypertension known 4 yr.; albumin and casts in urine intermittently.
			57	Hypertension known 5 yr.; traces of albumin in urine intermittently.
			30	Latent glomerulonephritis; persistent albuminuria, few erythrocytes in urine.
2. Tests on other occasions concur in good function	34	No renal or vascular disease; mild diabetes		
3. No other tests, clinical history negative	34	Psychoneurotic; no renal or vascular disease	54	Functional colitis; no renal or vascular disease.
	51	Functional colitis; no renal or vascular disease		
4. Tests on other occasions concur in poor function	38	Acute glomerulonephritis	38	Acute glomerulonephritis.
	39	Acute glomerulonephritis	19	Acute glomerulonephritis.
	23	Chronic active glomerulonephritis		
	50	Hypertension known 6 yr.; renal infarct (?)		
5. History of renal or vascular disease without clinical renal insufficiency	27	Hypertension 11 yr., no albuminuria	39	Latent glomerulonephritis; albuminuria and hematuria persistently.
	29	Mitral stenosis; traces of albumin in urine; no evidence of myocardial insufficiency	68	Generalized arteriosclerosis, Stokes-Adams syndrome; 1 urine negative; died.
	53	Hypertension more than 10 yr.; no albuminuria	62	Hypertension at least 5 yr., encephalomalacia; traces of albumin in urine intermittently.
	64	Arteriosclerosis; anemia, probably primary; albuminuria constantly	59	Hypertension known 3 yr., cerebral hemorrhage; traces of albumin in urine intermittently.
	47	Hypertension known 3 yr.; occasional trace of albumin in urine	50	Hypertension known 5 yr.; urine always normal, concentrates to 1.030.
			64	Arteriosclerosis, systolic hypertension; traces of albumin in urine intermittently.

TABLE 3.—CORRELATION COEFFICIENTS.

Mean clearance—1-hour ferrocyanid	0.712
Mean clearance—2-hour ferrocyanid	0.690
Mean clearance—3-hour ferrocyanid	0.713
First hour clearance—first hour ferrocyanid	0.718
Mean clearance—second hour ferrocyanid (expressed as a fraction of the remainder after first hour)	0.588

Discussion. Evaluation of a renal function test may well be approached from two standpoints. A knowledge of the physiology of the test makes it possible to make certain deductions as to the significance of variations; on the other hand a knowledge of the

other clinical findings with which the results are associated is required to establish the correctness of the deductions. It is also desirable to determine whether the procedure itself affects renal function; whether the procedure is safe; and whether it is simple enough for general use.

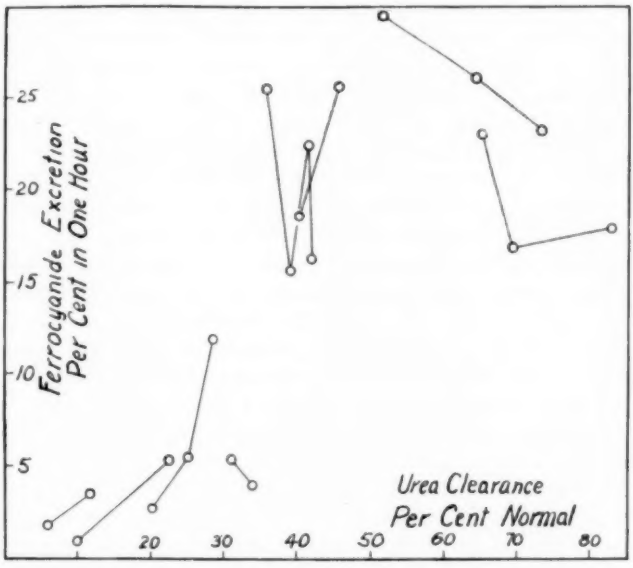

FIG. 2.—Mean clearance and 1-hour ferrocyanid excretion in repeated tests on 8 subjects.

On the theoretical side, the chief point of interest is the relation of the test to the amount of glomerular filtration. A satisfactory measure of glomerular filtration must fulfill four requirements: (1) the substance used must be eliminated by glomerular filtration and in no other part of the urinary tract; (2) it must not be reabsorbed in any part of the urinary tract; (3) the amount eliminated in the urine in unit time must be measurable; and (4) the concentration in the plasma during that time must be measurable.

It is probable that ferrocyanid satisfies the first two requirements sufficiently for practical purposes. Marshall[6] and Marshall and Grafflin[7] observed that aglomerular fish excreted ferrocyanid in insignificant amounts. Gersh and Stieglitz[8] produced histochemical evidence indicating that in the rabbit ferrocyanid excretion is glomerular and that reabsorption in the tubules is either absent or nearly so. Van Slyke, Hiller, and Miller,[9] using large doses of ferrocyanid intravenously, have demonstrated a plasma ferrocyanid clearance in the dog which parallels closely the simultaneous clearances of creatinin and inulin. Such close correspondence

among three substances so different chemically introduces a strong presumption in favor of exclusively glomerular elimination and lack of reabsorption.

Estimation of ferrocyanid in the urine presents no serious difficulties as a rule The fourth requirement is not fulfilled in this test. The concentration in the plasma is not, however, entirely uncontrolled; for the relation of body size to the size of the dose injected is important in determining concentration. A certain degree of constancy in plasma concentration can be assumed, subject to variations in plasma volume, body fluid volume, rate of diffusion, extrarenal elimination, and destruction of ferrocyanid. Variations correlated with differences in body size, furthermore, tend to be compensated in a very rough way by differences in kidney size.

It is therefore concluded that the rate of glomerular filtration is a factor in determining the rate at which ferrocyanid is eliminated following the intravenous injection of a known dose. However, the evidence so far fails to establish the rate of excretion under such conditions as a specific test of glomerular filtration.

Clinical evaluation of the test could be carried out ideally by observing a series of patients with progressive renal disease over a period of years and noting the clinical and anatomical phenomena with which changes were associated. This has been done for the urea clearance by several workers, of whom only a few need be cited here: Møller, McIntosh and Van Slyke[2] and Van Slyke, *et al.*[10] for the clinical, and Hayman and Johnston[11] for the anatomical changes. In view of the firm basis on which the urea clearance rests as a test of renal function, a comparison of the ferrocyanid excretion with the urea clearance is justifiable for an immediate estimate of its significance.

The graph (Fig. 1) indicates a definite relation between the levels of the two tests. While the choice of a definite lower limit of normal is an arbitrary procedure, a tentative limit may be set as a point of departure in further analysis. It appears from the graph that 24% excretion of ferrocyanid in 1 hour corresponds approximately to 70% of normal clearance in this series. If 24% be taken as a lower limit of normal, in 72 tests the urea clearance and the ferrocyanid excretion are concordant in revealing either normal or diminished function. These patients are sufficiently classified and require no further discussion.

The 30 discordant tests are equally divided between those in which the urea clearance is below 70% and those in which the ferrocyanid excretion is below 24% (Table 2). In view of the fact that the standards of normal are arbitrarily chosen, 9 may be dismissed as borderline cases in which the discordance is more apparent than real (Group 1). In Groups 2 and 3 it appears that the test giving higher results, and in Group 4 the test giving lower results, is more credible. The tests in Groups 2 and 4 were repeated at short inter-

vals and in no case was there evidence of change in the condition between tests. It will be observed that added evidence supports the urea clearance 5 times and the ferrocyanid test 5 times where there is discordance. Group 5 includes those in whom the evidence is still inadequate for judgment as to which test to believe. Three of the 5 with low clearance, and 4 of the 6 with low ferrocyanid output had albuminuria. The others with low clearances had had hypertension more than 10 years. Group 5 as a whole is clinically a borderline group.

From the comparison of ferrocyanid excretion with the urea clearance and with a view to other findings it is concluded that in the majority of instances patients with renal impairment excrete ferrocyanid more slowly than normal subjects and that the diminution parallels in a general way the diminution in urea clearance. If 24% in 1 hour be considered as approximately corresponding to 70% of normal clearance, the tests are about equally delicate in separating patients into two groups. In a minority of patients the result of either test may be satisfactory when the other is low, and the collateral evidence suggests that the error may be ascribed to either test with about equal frequency in this series. The present work offers no explanation of the physiologic significance of discordant results. The fact that the correlation of ferrocyanid excretion with clearance on the same specimen of urine is not significantly greater than its correlation with mean clearance suggests that the discrepancies are not to be ascribed in any considerable measure to irregularities in emptying the bladder.

Furthermore, it is too early to pronounce final judgment on the clinical significance of the ferrocyanid excretion test until it has been followed for long periods of time in single patients during the progress of renal disease. The value of the test in detecting impairment of renal function may well be considerable without similar value in estimating degree of impairment. The urea clearance has proved particularly valuable in that it is, on the one hand, relatively delicate in detection of impairment; and on the other, applicable to determination of changes in function through a wide range of values practically to the lowest function compatible with life. Progress may be observed in the clearance after the phenol red and specific gravity tests have reached a constant minimum. The accuracy of the ferrocyanid test in observing the progress of renal disease has not been established; not has its applicability been established where excretion is too low to be measured by the titration method used.

Several incidental observations on the test seem worthy of mention. The administration of ferrocyanid does not apparently affect the clearance; the clearance levels in normal subjects in this series cover about the usual range, and there was substantial agreement between the urea clearances with and without ferrocyanid in 32

subjects. There is no need for collection of urine specimens for more than 1 hour, in view of the similarity of correlation coefficients for various times; it may be that the collection period could advantageously be even shorter. The usefulness of the test is seriously limited in two important classes of patients, namely, those with prostatism and those with pronounced hematuria; in the latter group the difficulty is not insurmountable as a rule, but an accurate measure of ferrocyanid cannot be made by the present copper-sulphate method if much hemolysis has occurred. Aside from this difficulty the test is extremely simple and requires no apparatus other than that commonly possessed by any laboratory, nor any skill other than that possessed by the ordinary physician. For this reason the ferrocyanid excretion test promises usefulness particularly for office practice or under conditions where laboratory facilities are limited.

Summary and Conclusions. The ferrocyanid excretion test of renal function was compared with the simultaneous urea clearance in 102 subjects with a range of clearance levels from 6 to 130%. Following intravenous injection of 0.28 gm. of sodium ferrocyanid, normal subjects excreted at least 24% in 1 hour, 35% in 2 hours, and 50% in 3 hours. There was a correlation of about 0.7 between urea clearance and ferrocyanid excretion for each of these three periods. One hour proved to be an adequate length of time for the test. The administration of ferrocyanid did not alter the clearance. In those instances in which the tests gave discordant results other evidence pointed to error in each of the two methods with about equal frequency. The physiologic significance of the test is discussed. Considerable value in detection of impairment of renal function may be expected of the ferrocyanid test, but its value in observing the progress of renal disease cannot be judged yet and is somewhat more uncertain. The test is simple and harmless in most instances. Great care is required in estimating ferrocyanid in the presence of hematuria and some accuracy is sacrificed if much blood is present in the urine. Patients with prostatic hypertrophy had dysuria and inability to void in some instances.

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THE PHOSPHATID CONTENT OF ALBUMINOUS URINE.

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Phosphatids are believed by Hardy,[1] Chick,[2] Macheboeuf,[3] Went and Faragó,[4] Went and Goreczky,[5] Turner and Gibson,[6] and others to be associated with protein in blood. If a protein-phosphatid combination, physical or chemical, exists in the plasma, one might expect that the proteins excreted by patients with Bright's disease would carry their associated phosphatids with them into the urine. The present work was designed to ascertain whether the phosphatid-protein ratio in the urine of nephrotic patients is comparable to that in the plasma.

Methods. *Recovery of Phosphatid Added to Urine.* Ten cc. of an aqueous emulsion of cephalin from human brain, containing 2.12 mg. of lipid phosphorus, were added to 500 cc. of urine, containing 0.99% of protein. This was concentrated under vacuum (40° C.) to 15 cc., 300 cc. of alcohol ether (1 to 3 mixture) added, refluxed for 1 hour, filtered, evaporated almost to dryness (40° C.), extracted with several portions of petroleum ether and made up to 100-cc. volume. One cc. of this extract was used for the phosphorus analysis. Analyses were done in duplicate. Lipid phosphorus was determined by the method of Kirk.[7]

Another portion of the urine without addition to cephalin was treated in the same manner. Five cc. were employed for phosphorus analysis.

Petroleum-Ether-Soluble Phosphorus in Normal and Albuminous Urine. First Method. Five hundred cc. of urine were concentrated under vacuum to 50 cc., refluxed with 30 volumes of *alcohol-ether* mixture (3 to 1) for 1 hour and filtered. The filtrate was evaporated just to dryness below 60° C., and the residue was extracted with several portions of petroleum ether. The extracts were combined and made up to 100 cc. Ten-cc. portions were used for analysis.

Second Method. Protein was precipitated by treating lots of about 5 liters with 100 gm. of trichloroacetic acid and heating the mixture to 38° C. for 2 hours.

The *precipitate* was filtered off, washed with 1 liter of water, refiltered,

mixed with 10 volumes of alcohol-ether mixture (3 to 1), and refluxed for 12 hours. After filtering off the solvent, the residue was again mixed thoroughly with alcohol ether and refiltered. The combined filtrates were evaporated almost to dryness at 30° C. under vacuum, and the residue refluxed with redistilled ether for 30 minutes. The insoluble residue was treated with ether twice. The ether filtrate was filtered through fat-free filter paper, evaporated at 30° C., and the residue redissolved in boiling petroleum ether.

TABLE 1.—PETROLEUM-ETHER-SOLUBLE CARBON, PHOSPHORUS AND NITROGEN IN NORMAL AND ALBUMINOUS URINE.

Source of urine.	Protein content of urine, gm. per l.	P-E-soluble phosphorus, mg. per l.	P-E-soluble nitrogen, mg. per l.	P-E-soluble carbon, mg. per l.	Material extracted with lipid solvents.
		METHOD NO. 1.			
Nephrotic stage of nephritis	12.6	...	...	88.0	Total urine.
Nephrotic stage of nephritis	16.4	...	...	114.0	Total urine.
Nephrotic stage of nephritis	10.0	0.305	...	...	Total urine.
Normal	0	0.013	...	...	Total urine.
Normal	0	0.054	...	...	Total urine.
Malignant nephrosclerosis	1.8	0.306	...	...	Total urine.
		METHOD NO. 2.			
Nephrotic stage of nephritis	21.5	0	0.14	...	Precipitated urine protein.
Nephrotic stage of nephritis	...	0	2.80	...	Protein-free urine extract.
Nephrotic stage of nephritis	12.1	Trace	0.45	...	Precipitated urine protein.
Nephrotic stage of nephritis	...	Trace	0.07	...	Protein-free urine filtrate.*
Nephrotic stage of nephritis	10.2	Trace	Trace	...	Precipitated urine protein.†

* Protein-free filtrate was neutralized with ammonia hydroxid before concentration.

† Urine protein was dried at 35° C. then pulverized until it passed a No. 40 mesh sieve. The powder was extracted in a Soxhlet extractor for 24 hours with ether, followed by 24 hours' extraction with petroleum ether. After concentration of the extract to 100 cc., acetone was added (200 cc.) and the mixture placed in the ice box for 12 hours. A very slight precipitate resulted which redissolved in ether. Only traces of nitrogen and phosphorus were found in this solution.

The urine *filtrate* after precipitation of protein was concentrated at 35° C. under vacuum to 600 cc. This was placed in a continuous fluid extractor and extracted with ether for 8 hours. The extract was evaporated and the resulting oily residue dissolved in petroleum ether.

Petroleum-Ether-Soluble Carbon in Albuminous Urine. Six-cc. samples of urine from 2 patients suffering from the nephrotic stage of chronic nephritis were analyzed by the method of Kirk, Page and Van Slyke.[8]

Petroleum-Ether-Soluble Nitrogen in Albuminous Urine. Lipid nitrogen was determined by the micro-Kjeldahl method, using the new hypobromite reagent of Van Slyke and Kugel,[9] as described by Kirk, Page and Van Slyke.

Results. Recovery of petroleum-ether-soluble phosphorus in the form of cephalin added to albuminous urine was 79%. The quantities of petroleum-ether-soluble carbon and phosphorus in normal and albuminous urine are given in Table 1.

Conclusions. Nephritic patients losing large amounts of protein in the urine excrete only traces of lipid phosphorus (phosphatids) and lipid nitrogen. Lipid carbon is present in very small amounts.

Lipid phosphorus does not increase in the urine with increase in its protein content.

It appears that either phosphatids are not attached to proteins in the plasma in significant amounts, or that the combination is broken when the proteins are excreted in the urine.

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ACUTE POSTOPERATIVE NECROSIS OF THE LIVER.*

(SOCALLED HIGH-TEMPERATURE LIVER DEATH SYNDROME.)

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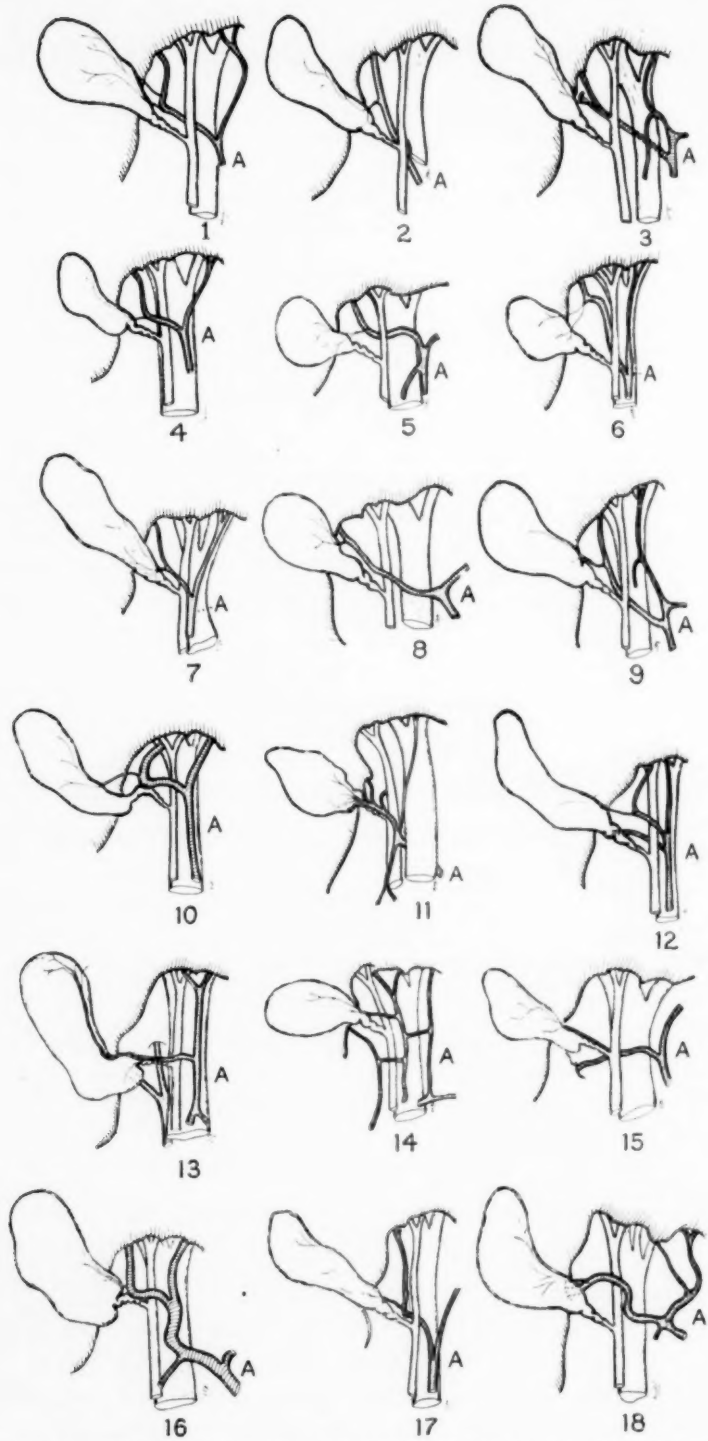
IN a preliminary report[1] attention was called to the essential clinical features and the lesion in the livers in patients who develop the so-called high-temperature liver death syndrome, and the similarity of the clinical course and liver damage in man dying with this syndrome and in dogs following ligation of the hepatic arteries was noted.

Heyd[2] first described this postoperative complication which is characterized by sudden, rapid and progressive rise in temperature during the first day after operation, falling blood pressure, rapid pulse, circulatory collapse, coma and death, with a temperature of 107° to 109° F., within 36 to 48 hours. Postmortem examination shows passive congestion, softening, diffuse disorganization of the

* Read before the New York Academy of Medicine, Section of Surgery, April 5, 1935.



FIGS. 1 to 29.—Sketches of dissections of the gall bladder, bile ducts and hepatic artery.
A, artery.

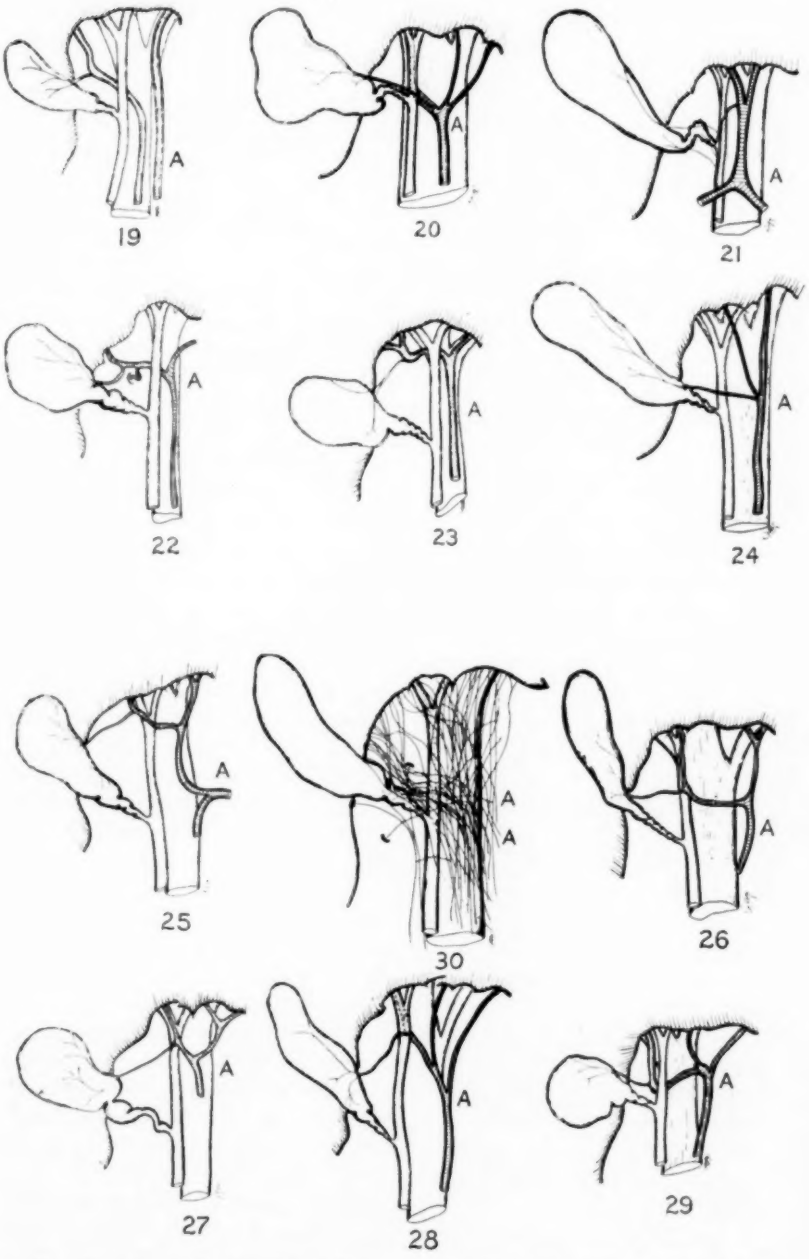


FIG. 30.—Composite drawing of Figs. 1 to 29. The single lines, *AA*, about the portal vein, bile ducts and cystic duct represent the locations of the branches of the hepatic artery in the 29 dissections.

liver cords with widespread areas of focal necrosis of the liver. From an examination of 23 livers following this type of "liver death," Boyce[3] concludes that in most instances when the clinical course was typical the postmortem findings were typical., *i. e.* necrotic changes in the liver with or without similar changes in the convoluted tubules of the kidneys, depending upon how long the patient lived after operation.

Henschen,[4] in his monograph on the meaning of the liver in surgery, in writing of this postoperative complication, says it is almost conceivable to him that this condition may be due to incidental ligation of the hepatic artery during the course of the operation. Thoreck[5] believes that 33% of individuals possess accessory hepatic arteries which may be a source of danger. Many investigators have studied the arrangement and distribution of the hepatic vessels and all agree that wide variation is common. The orthodox description found in anatomic texts leads one to believe that the hepatic artery passes toward the liver medial to the common bile duct and anterior to the portal vein; that it divides near the hilum of the liver into a right and a left branch which go to the respective lobes of the liver; and that the cystic artery normally arises from the right branch, passes to the right dorsal to the common hepatic bile duct and thence to the gall bladder. In this arrangement there would be relatively little danger of injuring an hepatic artery while clamping or dissecting the cystic duct.

In dissections of 29 unselected cadavers in the medical and the nurses' training schools during the past year, wide variation in the course and branches of the hepatic arteries was found (Figs. 1 to 29); and in 16, more than 50%, the right hepatic artery was in such close relation to the cystic duct that it might easily have been injured during a cholecystectomy. A composite drawing (Fig. 30) shows graphically the assembled relations of these arteries to the cystic duct.

To determine experimentally the clinical course and the liver changes following ligation of the hepatic arteries 14 dogs were operated upon. Cholecystectomy was performed in all and at the same time dissections were carried out isolating the hepatic arteries. The largest artery was invariably ligated and in many, smaller vessels were also clamped. All of the animals recovered promptly from their ether anesthesia, drank water freely, walked about their cages, responded normally and appeared to be in excellent condition. Six of these dogs developed immediate progressive rise in temperature, which reached 104° and 105° F. (Fig. 31). Five died in less than 36 hours and 1 died during the fourth postoperative day. Although fever reactions are more difficult to obtain in dogs than in human beings, the clinical postoperative course of these dogs was similar to that seen in high-temperature liver death syndrome. In all of the 6 dogs the livers showed diffuse disorganization of the

liver cords and many areas of focal necrosis (Fig. 32). These lesions resemble closely those found in human livers (Fig. 33).

Loeffler,[6] in reporting further investigations of the results of ligation of the hepatic arteries, concludes that the results are the same in man, the dog and the rabbit . . . . and it is immaterial at what point ligation occurs.

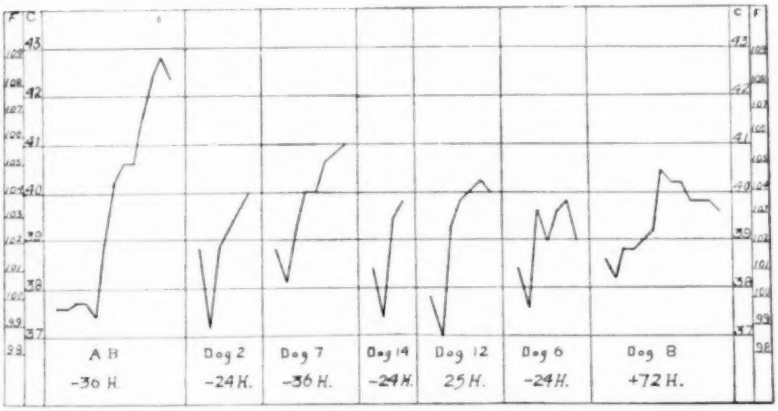


FIG. 31.—A. B. Patient who developed typical syndrome and died in less than 36 hours with the temperature shown. Photomicrograph of his liver, Fig. 33. Dogs 2, 6, 7, 12 and 14 after a fall of temperature during the operation showed progressive ascending temperature and died as the figures under the curves indicate. Dog 8 after showing immediate elevation of temperature lived for slightly more than 72 hours after operation.

In the 8 surviving dogs, none of which showed typical elevations of temperature, injections of a bismuth suspension or a starch mixture demonstrated adequate collateral circulation to all lobes of the liver. In these livers there were areas in which there was disorganization of the liver cords but there was no necrosis. Von Haberer[7] found in a large series of experiments in which he ligated the hepatic arteries that the animals which lived following the operation were those which possessed this collateral circulation.

Following operations upon the thyroid, in extensive burns and in intestinal obstruction there is occasionally a postoperative course clinically similar to that of high-temperature liver death syndrome. In these cases, while the liver is not involved in the operative procedure, there is hepatic softening and necrosis resembling that found after postoperative liver deaths.

In the presence of chronic and acute cholecystitis and biliary tract disease there are variable degrees of liver damage and operative trauma to the liver or vessels may be sufficient to cause the development of this syndrome. Direct injury to hepatic vessels is a frequent possibility and there might be accidental ligation or trauma

initiating thrombosis. Much work remains to be done, and the pathologist at the postmortem table by careful examination of the hepatic vessels at the hilum and in the substance of the liver may be able to throw additional light upon this problem.

The essential lesion in these "liver deaths" appears to be acute central necrosis of many liver lobules. Renal changes were not found in the experimental animals considered in this paper or in human patients who died within 48 hours of operation. Such kidney damage is secondary to the liver necrosis and requires more time for development. A clinical postoperative course similar to that found in human beings and similar liver changes can be produced in dogs by ligation of the hepatic arteries. While, clinically, vascular occlusion may be due to thrombosis, embolism, or accidental ligation, there are without doubt other as yet unknown factors which bear upon the development of this syndrome. In view of the similarity between the clinical course and liver changes in the experimental animal and in the human beings who develop this postoperative complication, it seems reasonable to apply a pathologically descriptive phrase and call it "acute postoperative necrosis of the liver."

Summary. 1. So-called high-temperature liver death syndrome is a clinical entity characterized by rapid progressive development of high fever, falling blood pressure, circulatory collapse, coma and death with a temperature as high as 109° F. within 36 to 48 hours after operation.

2. The essential lesion in the liver is diffuse central necrosis of the liver lobules.

3. Similar clinical courses and similar liver changes have been produced in 6 of 14 dogs by ligation of the hepatic arteries.

4. In 8 dogs which did not die with this syndrome there was adequate collateral circulation to all lobes of the liver and there was no hepatic necrosis.

5. The similarity in the clinical course and the pathologic changes in the liver in man and dog makes it reasonable to apply a pathologically descriptive phrase and call this postoperative complication acute postoperative necrosis of the liver.

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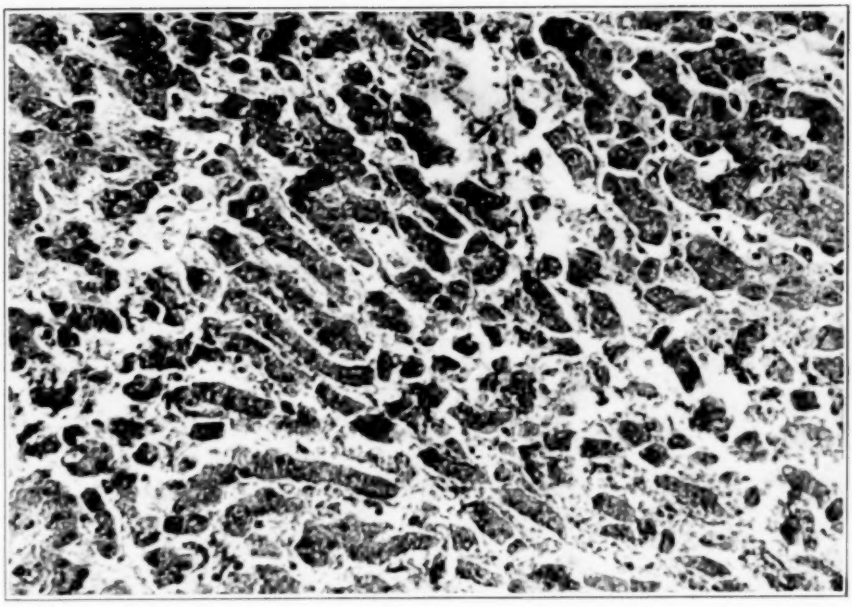

FIG. 32.—Photomicrograph of liver of Dog 7 fixed immediately after death. Note the disorganization of the liver cords and the necrotic liver cells.

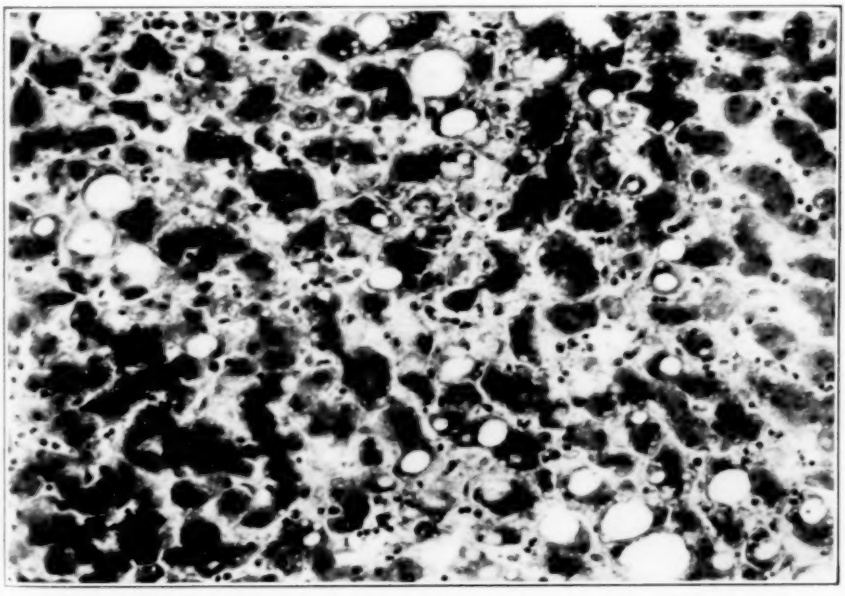

FIG. 33.—Photomicrograph of human liver (patient A. B.). Postmortem examination 1 hour after death. Note the disorganization of liver cords and necrotic liver cells.

ACUTE EPIDEMIC ENCEPHALITIS.

A Clinical Study of 160 Cases.*

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During the past two decades outbreaks of encephalitis have been reported at various intervals. They have been variously termed encephalitis, encephalitis lethargica, encephalomyelitis and meningoencephalitis. In general, the non-purulent encephalitides have been classified as follows:[9]

I. Type A encephalitis, or encephalitis lethargica (encephalitis of Economo).

II. Type B encephalitis or epidemic encephalitis (Japanese form and St. Louis form). Our present group of cases fall into this type.

III. Post- or parainfectious encephalitis. This includes measles, mumps, whooping cough encephalitis, etc.

IV. Other forms of encephalitis, such as postvaccinial encephalitis.

Following the influenza epidemic in Italy[9] during 1889–1891, a disease known as nona was described. This simulated, to a great extent, a postinfluenzal encephalitis that was so common during the interval of 1915 to 1925. Von Economo described the typical postinfluenzal encephalitis lethargica in 1916. During the 1915–1925 period, a large number of this type of cases were reported. This is an entirely different form than that which occurred in St. Louis and other epidemics of Type B form.

Several epidemics of Type B[2,9] have occurred in different parts of the world; but no large epidemic occurred in this country until the St. Louis epidemic in 1933. Japan has had frequent outbreaks. An epidemic occurred in Australia in 1917. No outbreaks of this type have been reported in Europe. In the United States, there were 4 distinct epidemics prior to the present one, but it reached large proportions only in St. Louis, with about 1100 cases. During the fall and winter months of 1919 to 1921, 78 cases were reported in Spokane, Wash. In Indianapolis, Ind., in 1930, 1931 and 1932, a curious outbreak was reported, which was described as meningoencephalopathy. In Paris, Ill., in 1932, 27 cases of encephalitis were reported.

It is our purpose in this paper to describe an epidemic of acute encephalitis that occurred in the Windber, Pa., district during the summer months of 1935. The epidemic began on or about July 14, was at its height from July 27 to August 5, and waned until Septem-

* Read at the Meeting of the Pittsburgh Neurological Society, November 18, 1935.

ber 15, when the last case was seen. During this time we observed 160 cases.

The chronologic history of the epidemic is interesting:

Case Abstracts. The first definitely diagnosed case, seen July 14, 1935, was an adult male, aged 25, who was suddenly seized with pain in the left eye, severe headache and stiffness of the neck. About 6 hours after the onset of these symptoms, he was admitted to the Windber Hospital. Examination upon admission showed the patient to be semistuporous; there was marked cervical rigidity and a bilateral Kernig sign. Spinal puncture showed the fluid to be clear, under increased pressure, positive for globulin, and there was a cell count of 2 cells per c.mm. His headache persisted for 1 week, and he complained of occasional vertigo during this time. Spinal puncture, on July 27, showed 8 cells. He was discharged from the hospital in good condition on July 29. Reëxamination, on September 25, showed patient to be in good condition and to be free from any subjective complaints.

The second case, a male, aged 13, was seen on July 19. This was the only fatal case, and we were fortunate enough to obtain an autopsy. The onset was sudden. There was a history of the patient having been swimming on the afternoon of his admission to the hospital. While in the pool, he complained of a severe headache and blurring of vision. He went out of the pool and rested. Very soon afterward he became comatose, and was brought to the hospital in this condition about 5 hours later. There was marked cervical rigidity and a bilateral Kernig sign. There was a spastic paralysis of the right arm and right leg. Spinal puncture revealed a bloody spinal fluid under greatly increased pressure. He died 2 days after admission. Autopsy showed a hemorrhagic meningoencephalitis. (For details, see discussion of pathologic anatomy.)

During the next 2 weeks the epidemic assumed widespread proportions throughout the community. A brother of the patient who died developed the infection on July 25. On July 30, at the height of the epidemic, we saw 15 cases. During the second week of August it began to wane, and the last case was seen on September 15.

Etiology. The disease is undoubtedly a virus infection. During the St. Louis epidemic, Muckenfuss, Armstrong, and McCordock[3] isolated a filtrable virus from glycerinated brain tissue of fatal cases. They were able to reproduce the disease in monkeys and mice. As our cases did not seem to be as virulent as the St. Louis type, it was felt that this type might be due to another strain of virus. The disease simulates influenza to a great extent, and one might even consider the fact that it is an influenza-like infection with a neurotropic rather than a pneumotropic virus. The virus must also differ from the one that causes encephalitis lethargica, as the clinical picture and pathology of these two conditions is entirely different.

Epidemiology. The disease is apparently transmitted by human contagion by means of droplet infection. It is very highly contagious and entire families are frequently affected; we have encountered instances in which 4 members of one family were affected. Residents of certain isolated districts of the community developed

the infection within a few days of each other. All of the patients had definite throat changes, tending to corroborate the idea that it is primarily a respiratory disease.

As nearly as could be determined, the incubation period varied from 3 to 10 days; in most cases it was about 4 days. In 1 instance a father developed the disease fully 2 weeks after a child had it, but we felt that his was probably a fresh exposure. In some in-

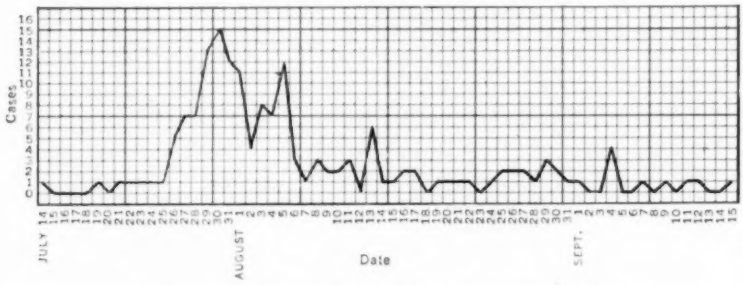

CHART 1.—Distribution of cases according to date of onset.

stances one member of a family would develop symptoms within 1 day after a previous member had developed the disease; but these were probably due to simultaneous exposures. In general, it seems safe to say that the incubation period varied from 3 to 10 days.

Season seems to have a definite influence upon this type of infection. In practically all of the other epidemics the highest incidence was during the late summer and early autumn months.

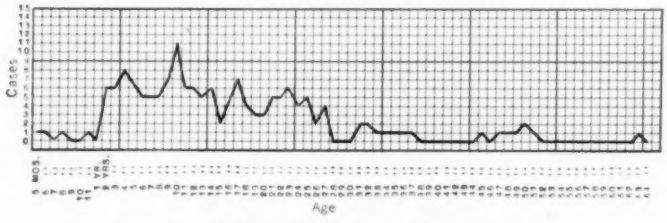

CHART 2.—Distribution of cases according to age.

The infection occurred more in males (98 males and 62 females). Most of the cases occurred in children and young adults; only 17 cases occurred after the age of 30. Young infants seemed to be immune; we encountered only 6 cases in infants under 2 years, and the youngest was aged 5 months. In an effort to determine whether young infants might not be affected with the disease and have vague symptoms, we did spinal punctures on a number of young infants who presented intestinal symptoms, such as vomiting and diarrhea or who had unexplained elevation of temperature. In all

of these cases the spinal fluid examination was negative. In this respect, encephalitis resembles other virus diseases, such as measles, young infants under 6 months being immune, as a rule. The oldest patient in the series was 63 years.

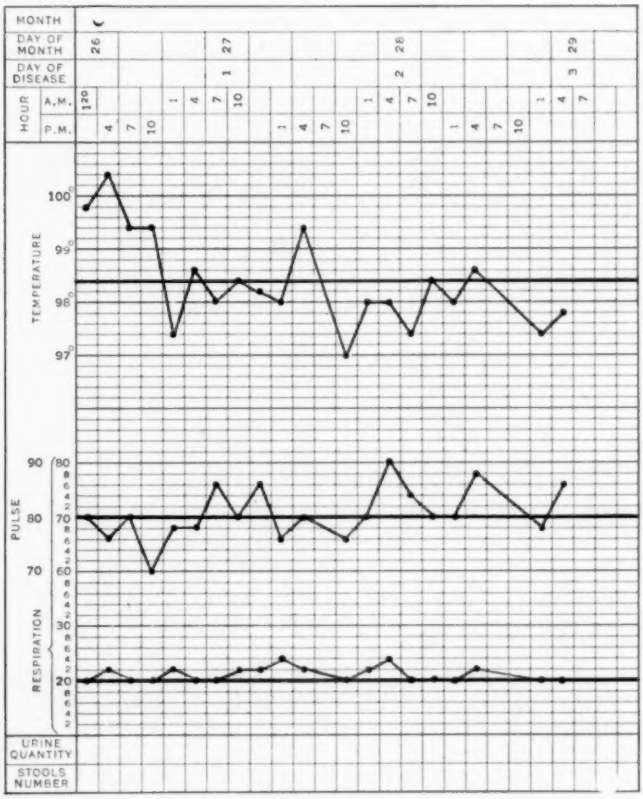

CHART 3.—Temperature, pulse, and respirations of a typical case.

Symptomatology. There was very little variation in the symptoms. Headache and nausea or vomiting were the outstanding symptoms. In a typical case the patient would be seized with a sudden severe headache followed in a few hours by nausea and perhaps vomiting. All of the children had persistent vomiting; many of the adults had only nausea. The headaches were usually occipital and the patients described them as being more severe than any other headaches which they had previously experienced. They also frequently complained of photophobia, pain in the eyeballs, pain in the posterior cervical region, backache, abdominal cramps, muscular pains, nervousness, sleeplessness and vertigo. Muscular pains were encountered very frequently; the vertigo was frequently

persistent and one of the last symptoms to disappear; the abdominal cramps would occasionally simulate an attack of appendicitis. Many patients were relieved of their symptoms while in the recumbent posture, but developed headaches or vertigo while sitting up, or upon any sudden change in posture.

In only 1 case were there convulsions or coma. This was the only fulminating case and the only one in which death occurred.

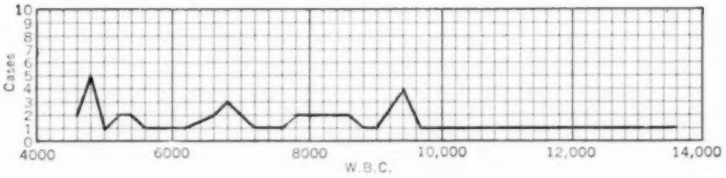

CHART 4.—White blood count in 38 cases.

Physical Signs. In general, there was a notable absence of positive physical signs. Most of the patients did not have any cervical rigidity or positive Kernig sign. In a few of the severe cases with a greater degree of meningeal involvement there was mild cervical rigidity and a moderately positive Kernig sign. Occasionally the pupils were irregular. There were no changes in the abdominal reflexes. One constant positive finding was the typical injection of the soft palate. The soft palate was reddened in all cases and presented a peculiar fine vesicular eruption, giving a strawberry-like appearance. The appearance of the throat differed entirely from that seen in the usual throat infections.

In a few instances there was impairment of the mental faculties. In 1 case there was a hemiplegia.

The temperature varied from normal to 102.4° F. In most cases it was about 101° F. upon admission, and would drop by lysis within 2 or 3 days. The pulse rate was usually slower than one would expect from the temperature record. In some instances there was a marked bradycardia, and in 1 case the pulse rate was as low as 24 per minute.

Blood Findings. There was usually a leukopenia (lowest leukocyte count, 4600). In many cases there was a normal count; in a few there was a moderate leukocytosis (highest, 13,600). There was no disturbance of the relationship of neutrophils to lymphocytes, this, as a rule, being normal.

Spinal Fluid Findings. The spinal fluid findings made on 32 patients, were important. We did not examine the spinal fluid in all cases, as many of the cases were too mild to be subjected to needless spinal punctures. However, during the first few days of the epidemic, spinal puncture was performed on all those suspected. We were amazed to find spinal fluid changes in many patients who

otherwise might be considered to be suffering from gastro-enteritis or a form of influenza. In all but 2 cases the fluid was clear; in 1 case it was opalescent; in 1 markedly bloody. The pressure varied; as a rule, it was increased (15 to 25 mm.); in some cases normal. Globulin was present in varying amounts in all cases. The cell counts were moderately increased; in a few cases they were normal, but in 22 they were over 20 per c.mm. Most of the counts were between 50 and 100; in 1 instance a patient had a cell count of 3 on admission, but 3 days later they had increased to 424; the highest was 670. The cells were 100% lymphocytes. The spinal fluid sugar was normal or slightly decreased.

TABLE 1.—CEREBROSPINAL FLUID CELL COUNTS IN 30 CASES OF EPIDEMIC ENCEPHALITIS. DIFFERENTIAL COUNT: 100% LYMPHOCYTES.

Cell count.	No. of cases.	By groups.	No. of cases.
1	1		
2	2		
3 (later 424)	1	Below 10	6
5	2		
12	1		
13	1		
23	1		
34	1	10 to 50	9
40	2		
42	1		
44	1		
47	1		
57	1		
60	1		
67	1		
68	1	50 to 100	9
70	1		
80	1		
87	2		
88	1		
105	1		
112	1		
117	1	100+	6
122	1		
355 (later 670)	1		
393	1		

Clinical Course. There were 3 types of the disease:

1. The mild or abortive type. In this type the patient would be seized with a sudden, severe headache, vomiting, and moderate elevation of temperature. Vomiting and the headache would subside within 24 hours, and the patient would be perfectly well at the end of 3 days.

2. The moderately severe, or usual type. In this type the initial symptoms were more severe. The patient sometimes presented a picture of collapse. Headaches would persist for possibly a week or more. The temperature would fall by lysis in about 3 days, but

the headaches and vertigo would persist for sometime afterward. This type was occasionally followed by persistent headaches for several weeks. Most of these patients, however, felt well at the end of about 1 week, and have remained free from symptoms thereafter.

3. The severe or fulminating type. Fortunately, there was only 1 case of this type. The onset was sudden; the patient rapidly became comatose, and died 2 days after the onset of symptoms.

Differential Diagnosis. The disease must be differentiated from the following:

1. *Influenza.* The symptoms of influenza frequently simulate the symptoms that we encountered in this epidemic. The headaches were more severe than those ordinarily encountered in influenza. The throat had a characteristic appearance that differed from influenza. Spinal puncture served as a final means of differentiation.

2. *Meningitis.* Symptoms of meningeal irritation were not as common as in meningitis. The spinal fluid pressure was not as great as in meningitis. Tuberculous meningitis usually has a more gradual onset, and does not result in cure as does this illness. It must be borne in mind, however, that most of these cases had some meningeal involvement also.

3. *Poliomyelitis.* The involvement in our cases was cerebral rather than spinal. In no case was there any residual flaccid paralysis. The spinal fluid changes simulated those of poliomyelitis to a great extent.

4. *Encephalitis Lethargica.* The symptoms and clinical course differed considerably from encephalitis lethargica. There was usually no lethargy and there were no postencephalitic sequelæ such as follow the lethargic type of encephalitis.

5. *Appendicitis.* Occasionally the abdominal pain and vomiting would lead one to suspect that the patient was suffering from an attack of appendicitis. However, there was usually no abdominal tenderness. Leukocytosis was usually absent.

6. *Acute Gastroenteritis.* It was difficult to differentiate the disease from gastro-enteritis in many instances, particularly in children. In doubtful cases, spinal punctures would reveal the diagnosis.

After the first group of cases were studied, we were able to establish a group of symptoms and findings which enabled us to diagnose most of these cases without resorting to a spinal puncture. These were as follows: (1) Severe headache and vomiting; (2) characteristic throat findings; (3) leukopenia; (4) history of exposure.

When a patient presented the above history and findings, we felt we were justified in making a diagnosis without unnecessarily subjecting him to a spinal puncture.

Pathologic Anatomy. A postmortem examination was made on 1 case.

Autopsy Findings (Dr. H. A. Slesinger): The dura mater was injected. The entire brain was edematous and its cut surface presented a pinkish color. There were numerous petechial hemorrhages throughout the cerebrum. There was a large area of hemorrhage in the posterior extremity of the thalamus; this had caused erosion into the lateral ventricle and the latter was filled with blood.

Histologic examination of the brain (Dr. R. D. Lillie):

"The leptomeninges present widened spaces without visible contents for the most part. In areas there is extravasation of considerable quantities of partially laked blood, accompanied by a few macrophages and occasional mantling of a small meningeal vessel by lymphocytes. In occasional sulci there is considerable perivascular and interstitial accumulation of neutrophils and lymphocytes.

"The anterior portion of the thalamus shows quite marked capillary congestion, rather numerous corpora amylacea (?) and slight lymphocyte infiltration in the sheaths of a few arterioles. Masses of densely and metachromatically basophilic material similar to the above 'corpora amylacea' occur also in the vessel sheaths in other similarly congested levels of the thalamus. These bodies are quite numerous in some markedly congested areas of white substance.

"In the posterior extremity of the thalamus, adjacent to the cut surface made in severing it from the brain stem there is a considerable area of hemorrhage into the brain substance, surrounding a small artery. Pericapillary hemorrhages are seen about the margins of this hemorrhagic area. Proliferative or inflammatory marginal reaction is absent.

"The hippocampus shows no Negri bodies or other inclusions.

"The corona radiata of the parietal to occipital regions contains several focal perivascular hemorrhages, sometimes of ring form with vessel necrosis centrally. An occasional arteriolar sheath in the occipital region is slightly infiltrated by lymphocytes.

"The gray cortex shows only a slight patchy capillary congestion. There are no lesions in the corpus striatum or corpus callosum.

"The findings are those of an acute hemorrhagic meningoencephalitis."

Prognosis. The prognosis was unusually good. There was 1 fatal case. Of the remaining cases, all but 7 were perfectly well within 2 weeks from the date of onset of their illness. The remaining 7 complained of various symptoms lasting from 3 weeks to 3 months.

Complications and Sequelæ. There were very few complications or sequelæ. There were no pulmonary, cardiac, or renal complications. Seven patients complained of residual symptoms. These included persistent headaches, vertigo, nervousness, sleeplessness, and weakness. At the present time only 1 patient in the entire group has any complaints. This patient, after a period of 3 months, still complains of occipital headaches and vertigo. His headaches

were severe for about 2 months; they are now gradually becoming milder. He has also developed a moderate degree of baldness following his illness. It is certainly too early to state whether or not there will be any delayed sequelæ such as occurred in the post-influenzal encephalitis. However, the experience in St. Louis was that there were no such sequelæ.[6]

Treatment. The treatment varied with the severity of the disease. In the mild cases the patients were treated symptomatically with salicylates and codein and kept in bed for 1 week. The more severe cases were kept in bed for 2 weeks. At first, we did spinal punctures routinely, but subsequent experience proved that those that did not have spinal punctures recovered just as rapidly as those that did. We then performed punctures only on those patients that had persistent headaches for more than 24 hours, or where there were definite signs of increased intracranial pressure.

About 10 days after the onset of the epidemic we started to use convalescent serum (administered intramuscularly) obtained from patients who had recovered from the illness. We used it both prophylactically and in the active treatment of the more severe cases. Twenty-two active cases received a therapeutic dose, which we arbitrarily placed at 7.5 cc. of serum. Although it is extremely difficult to evaluate the results, we felt that these patients recovered more quickly than those that did not have the serum. As stated above, only the more severe cases received the serum, and we found that they would improve at least 24 to 48 hours sooner than those that did not have the serum. None of these patients had symptoms persisting for more than 1 week. The results with serum therapy were more satisfactory if the patient received treatment within 24 hours after the onset of the illness. In 1 case, a child with definite findings of encephalitis was given a dose of serum and was perfectly well within 16 hours. In most of the other cases the patient would begin to improve within 12 hours after the administration of serum and be symptom-free within 24 to 36 hours. However, it must be remembered that many untreated patients also improved very rapidly.

We are positive that convalescent serum has a definite place in prophylaxis of the disease. Prior to the use of serum we were unfortunate enough to have two members of the hospital personnel develop the infection. After the serum became available, we administered 5 cc. of serum to 7 members of the medical and nursing staff who were most likely to be exposed; none of them developed the disease.

Summary. 1. The clinical features of an epidemic of acute encephalitis have been described; 160 cases were seen over a period of 2 months.

2. The disease was highly contagious. It ran a relatively benign course. There were very few residual symptoms.

3. Convalescent serum was of definite value both as a prophylactic measure and in the active treatment of the disease.

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FOREIGN PROTEIN THERAPY.

II. TREATMENT OF UNDULANT FEVER BY THE INTRAVENOUS INJECTION OF KILLED TYPHOID–PARATYPHOID "A" AND PARATYPHOID "B" BACILLI.

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THE object of this paper is to present a series of 12 cases which demonstrate the efficiency of foreign protein therapy in the treatment of undulant fever. The effectiveness of the intravenous administration of foreign proteins in the treatment of this disease has been widely discussed. The usefulness of such substances is assumed to depend upon factors associated with the sharp thermal reaction following their administration.

The treatment we have used with uniform success consists of the intravenous administration of mixed typhoid vaccine,* each cubic centimeter containing 1000 million typhoid bacilli and 500 million each of para typhoid bacilli "A" and "B". The initial dose of 50 million killed organisms was repeated every 5 days until 4 to 6 treatments had been given, the dosage being increased 25 to 50 million each time.

* Eli Lilly Company No. 3V765.

In 1918, Evans[1] demonstrated a close relationship between the serologic behavior of the organisms responsible for undulant fever and Malta fever, and since then these two diseases have been regarded as practically identical. The relationship between this infection in man and contagious abortion in cattle is quite striking, as most cases of undulant fever are traceable to close association either with infected cattle or the consumption of raw cow's milk from contaminated herds.

The incidence of undulant fever in the United States is steadily on the increase. We have seen 12 cases of clinically active undulant fever in the Geisinger Memorial Hospital during the past 5 years in 20,000 general admissions. The United States Public Health Service Statistics[2] for 1933 show a total of 1788 cases reported in that year and in 1934 there were 2017 reported. The records of the Bureau of Contagious Diseases for the Commonwealth of Pennsylvania[3] show 294 cases reported from 1929 to 1934.

The disease presents a fairly characteristic picture by the time medical aid is sought. The onset is variable in type and intensity, ranging from abrupt chills, fever, abdominal pain, nausea, vomiting, acute arthralgia to simple malaise with a low-grade fever which may be overlooked. Men are more often affected than women; 11 of our 12 cases were in men. The usual complaint on admission is weakness, nervousness, loss of weight, arthralgia, fever and epigastric symptoms of varying patterns. Examination of blood for specific agglutinins of *Brucella abortus* is most valuable diagnostically after 2 weeks of illness, although some observers feel that this test frequently remains negative throughout the course of the disease. The intradermal skin test with undulant fever vaccine is helpful in the latter cases. Axel Thomsen,[4] of Copenhagen, Denmark, found the complement-fixation test to be far more frequently positive than the agglutination tests.

The following case histories illustrate the findings and treatment in this series:

CASE 1.—R. F., white male, aged 8, entered this hospital, August 2, 1934, complaining of weakness, fever, malaise, anorexia, weight loss, generalized muscle soreness, headache and progressive stupor. The temperature fluctuated between 101 and 103. He was in a semistuporous state upon admission which was rapidly progressive for the first few days. He had a bilateral Babinski, fleeting bilateral ankle clonus, absence of abdominal reflexes on the right side. Initial spinal fluid examination showed 175 cells mostly small lymphocytes, 66 mg. sugar and 590 mg. chlorids. Twenty days after admission, his blood was positive for *Br. abortus* in a titer of 1 to 160 (see chart for temperature pattern). He was given his first treatment of 0.05 cc. typhoid mixed vaccine intravenously on the 15th day after admission. His temperature rose to 104° and returned to normal within 24 hours, remaining normal for several days when a slight recurrence was noted, so a second injection was given. Convalescence was rapid and dramatic. Within 24 hours after his first treatment the mentally lethargic state cleared rapidly. He was discharged from the hospital August 31, 1934, in good physical

condition. Check-up examination February, 7 1936, showed a normal child whose blood gave a negative reaction for *Br. abortus*. This case was of especial interest in view of his encephalitic manifestations.

CASE 2.—H. A. B., white male, aged 40, entered this hospital July 29, 1934, complaining of weakness, daily temperature elevation of 6 weeks' duration, of sleepless nights, chills and sweating on several occasions. This man was manager of several farms and was frequently thrown in contact with the dairy herds. Physical examination was irrelevant. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Before a diagnosis of undulant fever had been established, this patient was given 10 cc. of 1% mercurochrome intravenously and later 3 cc. of sterile skimmed milk intramuscularly. Following each injection he showed a rather sharp thermal rise but no lasting improvement. On the 10th day after admission he was given the first treatment of 0.05 cc. typhoid mixed vaccine intravenously (see temperature chart for reaction). Treatment was repeated, convalescence was uneventful and check-up examination February 5, 1936, showed a normal individual whose blood gave a negative agglutination for *Br. abortus*.

CASE 3.—A. R., white male, aged 62, entered this hospital May 29, 1931, with the chief complaint of weakness and "stomach trouble." Well until 6 weeks prior to admission when the symptoms of weakness and fever were first noticed. Weakness was progressive. A diagnosis of undulant fever had been established by his family physician. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Physical examination was irrelevant. Temperature fluctuated between 99° and 102°. He was given the first intravenous injection of typhoid mixed vaccine June 1, 1931, the second injection on June 6, the third on June 9, and following the last injection, temperature dropped to normal and remained so. He was discharged from the hospital June 29, 1931, symptom free. Check-up examination February 18, 1936, showed a healthy individual whose blood gave a negative agglutination for *Br. abortus*.

CASE 4.—L. G. K., white male, aged 54, entered this hospital January 22, 1930, complaining of weight loss amounting to 25 pounds and nervousness of 3 months' duration. Physical examination showed a warm, perspiring skin, moderate degree of emaciation, weakness and tremor of the muscles of the upper extremities and temperature which varied between 99° and 101°. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Two weeks after admission the patient had his first injection of 250 million typhoid organisms intravenously. The temperature immediately started to "flatten out" and remained normal after the third injection. Improvement was phenomenal. He was discharged from the hospital February 12, 1930. Follow-up examination November 2, 1935, showed the patient to be in perfect health and agglutination to *Br. abortus* negative.

CASE 5.—J. M., white male, aged 38, entered this hospital December 1, 1934, complaining of pain in the abdomen and chest, chills and fever at night of 2 weeks' duration. For 12 consecutive days he had a daily, hard, shaking chill followed by high fever with diffuse perspiration. Malaria was suspected. Physical examination was remarkably negative. Blood agglutination was positive for *Br. abortus* 1 to 40 on December 7, 1 to 80 on December 13, and 1 to 320 on January 4, 1935. He was given routine treatment of 0.05 cc. typhoid mixed vaccine intravenously and his temperature returned to normal after the second injection where it remained. He was discharged from the hospital December 28, 1934. Check-up examination July 31, 1935, showed a normal individual except for subjective pain in the right knee joint. Blood gave a negative reaction to *Br. abortus*.

CASE 6.—A. D., white male, aged 14, entered this hospital May 14, 1933, complaining of fever of 4 months' duration. Symptoms began as headache

and fever. Onset was abrupt and he was confined to bed for several days. He improved so he could be up and around but continued to have afternoon chills, fever and headache. His temperature often went to 104°. During the 4 months of illness the clinical course was characterized by periods of exacerbation and relief. His temperature after admission fluctuated from around 100° in the morning to 105° in the afternoon. He had a chill followed by high fever every afternoon for the first week after admission. On the 8th day, treatment was instituted when he received 0.06 cc. typhoid mixed vaccine intravenously. This patient was given 6 injections of typhoid mixed vaccine and some improvement followed each treatment but temperature did not return to normal until after the last injection. He was discharged from the hospital June 3, 1933, much improved. Further convalescence at home was uneventful. Follow-up examination January 7, 1936, revealed a normal boy whose blood gave a negative agglutination to *Br. abortus*.

Case 7.—H. B., white male, aged 50, entered this hospital April 17, 1935, complaining of chills and fever. Illness dated back to March 24, 1935, when he had his first chill followed by fever. Since that time he has had daily elevations of temperature. Agglutination for *Br. abortus* was positive in a titer of 1 to 320. Admitted to the hospital for typhoid vaccine therapy. His temperature returned to normal after the third injection. He had 0.05 cc., 0.075 cc. and 0.075 cc. typhoid mixed vaccine intravenously. His temperature dropped to normal and remained so. He was discharged from the hospital April 29, 1935. Agglutination for *Br. abortus* February 24, 1936, was positive but the patient has remained symptom free.

Case 8.—G. H., white male, aged 32, was admitted to this hospital September 18, 1933, complaining of afternoon fever of 5 weeks' duration. Onset was acute with aching throughout entire body. Confined to bed for 2 days. Up and around afterward. Not able to work. Had non-productive cough since onset of illness, worse upon arising in the morning. Physical examination showed a well-nourished individual, not ill apparently. Agglutination for *Br. abortus* was positive in a titer of 1 to 640. His temperature ranged from 99° to 101°. He could not remain in the hospital so he returned home on September 19, but was readmitted September 25 for treatment. He was given 5 intravenous injections of 0.05 cc. typhoid mixed vaccine on the following dates: September 26, 28, 30, October 3 and 7. His temperature returned to normal after the third injection and remained normal thereafter except during treatment. He was discharged from the hospital finally October 10, 1933. He has been symptom free since. Agglutination was negative for *Br. abortus* August 26, 1935.

Case 9.—W. H., white male, aged 53, entered this hospital from Devitt's Camp April 16, 1935. Diagnosed as acute undulant fever complicated by active pulmonary tuberculosis. Due to the fact that this patient was suffering from tuberculosis, he was given only 0.035 cc. mixed typhoid vaccine as a first dose and 0.025 cc. for the second, third and fourth. Temperature response was similar to those illustrated by Chart I. He was discharged from the hospital May 1, 1935. Follow-up January 28, 1936, reveals no symptoms referable to undulant fever but his agglutination for *Br. abortus* is still positive in a titer of 1 to 160. October 21, 1935 it was positive in a titer of 1 to 320.

Case 10.—A. B., white male, aged 40, was admitted to Devitt's Camp June 18, 1934. At that time his temperature was fluctuating between 99° and 100°. He was treated by pneumothorax and as a result his temperature gradually declined with only occasional exacerbations, reaching normal October, 1934, where it remained until February 1, 1935. Another exacerbation of temperature began at this time which persisted until March 2 when it began to subside. On March 19, 1935, he entered this hospital.

His blood showed a positive agglutination for *Br. abortus* in dilution 1 to 1280. While here, his temperature continued to drop and when he left the hospital March 25, it was fluctuating between 98° and 99°. After returning to the Camp, his temperature remained practically normal. This is an example of a patient suffering from undulant fever and active pulmonary tuberculosis who made an uneventful recovery without any special therapy. It has been suggested that perhaps the tuberculosis had some influence in the favorable termination of the undulant fever. On January 28, 1936, an agglutination test of the blood serum for *Br. abortus* was negative.

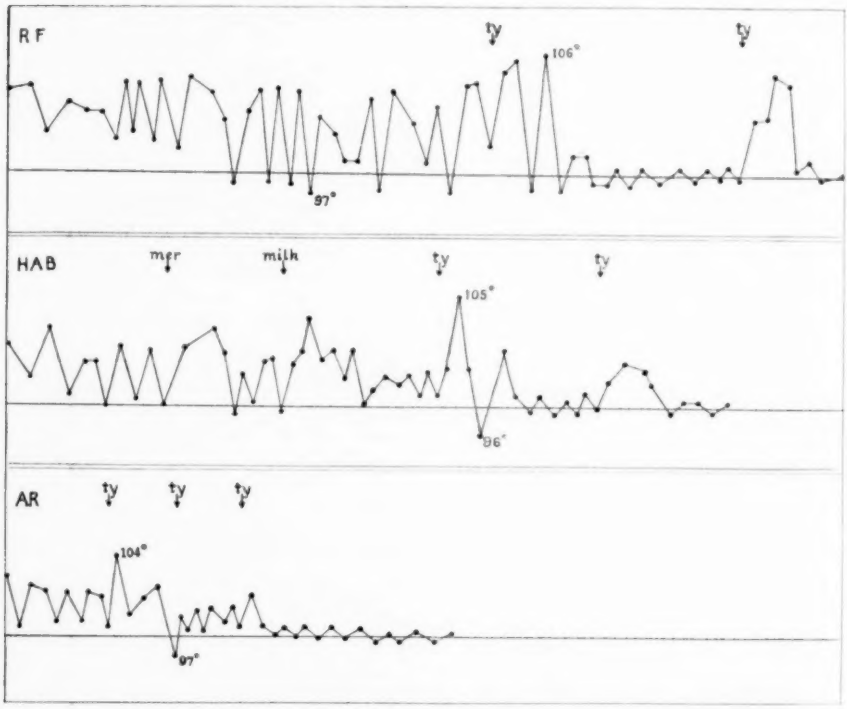

CHART I.—Fluctuations of temperature following the intravenous injection of killed typhoid and paratyphoid "A" and "B" bacilli. (Ty = injection of killed typhoid and paratyphoid organisms; Mer = mercurochrome.)

CASE 11.—J. K., a white male, aged 19, entered this hospital January 18, 1930. This patient ran a typical course of undulant fever with onset of symptoms December 21, 1929. He had a normal morning temperature but afternoon temperature rose to 102° or more. While in the hospital, temperature fluctuated between 99° and 101.4°. When he was discharged from the hospital January 27, 1930, the fever was not improved. He went home and has had no special therapy. He continued to have fever for 5 months after he returned home and his physician reported 5 years later that he had never returned to his normal health. He still complains of periods of fatigue, vague, fleeting pains in various parts of his body, heart consciousness, but he has had no recurrence of fever. This patient was under observation before the use of typhoid vaccine had been instituted. His convalescence undoubtedly could have been greatly shortened by this agent.

CASE 12.—D. L. S., white female, aged 51, entered this hospital August 22, 1935, complaining of pain in the legs and joints, "poor heart," cough, repeated attacks of fever and night sweats of more than a year's duration. Ten months before admission she had been confined to bed for 4 weeks with fever of unknown origin. In January, 1935, she was admitted to another hospital where a diagnosis of undulant fever was made. She remained in the hospital for 30 days but her symptoms continued. Physical examination revealed a poorly nourished woman prematurely senile, sunken eyeballs, red tongue, pusy tonsils, heart sounds of poor quality, inguinal hernia, rectocele and cystocele, slight swelling of the hands, especially of the second metacarpal phalangeal joints. Our first impression was that the patient had a malignant disease masquerading under the diagnosis of undulant fever. Agglutination for *Br. abortus* was positive 1 to 320. Her temperature was of an irregular pattern reaching a peak of 101.4°. She was given 0.05 cc. typhoid mixed vaccine intravenously on the 13th day after admission. This dose was repeated twice. Improvement was rather phenomenal except for the fact that she has continued to complain of pain in the joints. After the first injection she had a desire to get out of bed and began to take an interest in things about the ward. She was discharged October 8, 1935. Follow-up examination January 10, 1936, showed an agglutination test for *Br. abortus* was positive in a titer of 1 to 60. She was greatly pleased with improvement made to date, however. She was unquestionably a case of chronic undulant fever and we are glad to include her in this series.

Discussion. It is of interest to conjecture as to the manner in which such a non-specific substance as mixed typhoid vaccine influences the course of undulant fever. One is impressed by the fact that almost any substance which will bring about a sharp thermal reaction will act favorably on the infection of undulant fever. For instance, Debono[5] noted that after giving intravenously a filtrate prepared from Brucellin and Melitine that the temperature of the patient reached a maximum in 17 or 18 hours and then it came down the next day. He was able to bring the temperature down to normal after 2 or 3 injections of this material. It is noted in one of our cases, for instance, after the use of mercurochrome and skimmed milk, a favorable influence was exerted upon the fever. Our experience corresponds to the favorable results reported by Sinclair Miller.[6]

The mechanism of recovery is still a matter of speculation. In a previous article we reported that from the hemocytologic standpoint, the most significant changes which occurred following the intravenous injections of killed typhoid and paratyphoid bacilli were found in the total leukocyte count, the neutrophils, the metamyelocytes and the lymphocytes. These observations were made by obtaining a control count immediately preceding the injection of killed organisms. Following the injection of the killed typhoid and paratyphoid bacilli a complete blood count was made at hourly intervals for a period of 4 hours; 24 hours after the injection another complete blood count was taken. With few exceptions the blood counts were made by the same person and the differential counts in all instances were checked by one of us.

In the series of cases reported in this article a similar study was made of each patient's blood and in every instance following the injection of the killed organism a relative leukopenia occurred in the first hour followed by a return to the pre-injection level in the second hour. In the third and fourth hours there was a leukocytosis, followed by a drop to the pre-injection level after 24 hours. The neutrophil response closely paralleled the response of the total leukocytes. The metamyelocytes showed no initial increase but a steady increase during the first 4 hours.

The lymphocytes showed an increase in the first hour and a decrease in the following 3 hours. The postinjection 24-hour count revealed that the lymphocytes were near the pre-injection level.

All of the hemocytologic changes just described were transient as evidenced by the fact that at the end of 24 hours the findings were practically identical with the pre-injection observations.

While the observations reported in this study do not explain why the patients recovered, we do feel that inasmuch as they were infected with a specific organism (*Br. melitensis* or *Br. abortus*), the results obtained strengthen the theory that the injection of killed typhoid and paratyphoid bacilli stimulate a general non-specific immunogenic reaction. This reaction is reflected in the altered blood picture which indicates a response of the reticulo-endothelial system to the foreign proteins injected.

Such a response may in turn be the fundamental reaction which is responsible for the production of resistance or immunity. While we do not know exactly where antibodies are formed, our results suggest that the injection of killed typhoid and paratyphoid organisms is responsible for the production in the body of non-specific or specific antibodies of sufficient quality to enable the patient to overcome the disease. Of course, one cannot discuss immunity without considering the rôle played by the phagocytes in ridding the body of bacteria. In the problem dealt with in treating these patients, phagocytosis may have played an important part, but from the results obtained from animal experiments which we will report in a subsequent article, we are convinced that the production of antibodies is the factor responsible for the patient's recovery.

Conclusions. 1. Of 12 cases of undulant fever observed, 10 were treated by the intravenous administration of typhoid vaccine. The results in all 10 were satisfactory. There have been no recurrences and the follow-up agglutination tests for *Br. abortus* were negative in 9 of the 10 cases treated. Two follow-up agglutinations in control cases were also negative.

2. These results compare favorably with the treatment reported by other authors who have used specific substances prepared from *Br. abortus*.

3. The distinct advantages of typhoid vaccine are its availability in all localities and the simplicity with which it can be administered.

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NEPHRITIS IN GOUT.

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Aretæus, the Cappadocian, a contemporary of Galen, is given credit for first describing a scanty, deep yellow, cloudy urine during attacks of gout.[2] Thus, some seven centuries after the recognition of gout by Hippocrates, attention was directed to the kidneys. The red granular kidney of this disease has been commented upon and described through many centuries. Nephritis has been regarded as a common complication in gout, and there have been a number of isolated case reports in the literature, but statistics on the subject of kidney disease in gout, based on series of cases, are lacking.

The lesion in the kidney that has been described in gout is that of "interstitial nephritis" (nephrosclerosis or the arteriosclerotic kidney); in fact, "interstitial nephritis" has often been alluded to as the "gouty kidney." Rarely have uratic deposits in the kidney in sufficient amounts to produce renal impairment been encountered. Nephrolithiasis, long supposed to be a manifestation of gout, is now regarded as incidental. On account of the belief that albuminuria and decreased renal function are common in gout, the old question of impaired renal function as an etiologic factor in this disease is still a point of controversy. In only a few instances have pathologic studies shown normal kidneys in gout.

Vascular disease and hypertension are thought to be fairly common in gouty subjects,[1] but it must be remembered that the age period in which gout usually occurs is the one in which essential hypertension and arteriosclerosis are frequent. However, the literature suggests that nephritis is more common in this disease than is expected in non-gouty patients of a similar age. The origin of the nephritis has been assumed to be on a vascular basis.

In the course of another study on gout[2] we were struck with the

extremely high incidence of the additional diagnosis of chronic nephritis in the cases of gout in this hospital. In an analysis of these cases, which constitute the material for this study, we have attempted to determine an approximate incidence of nephritis in gout and to study the clinical and pathologic types of renal disease.

We have reviewed the records of 55 cases of true gout admitted to this hospital from 1913 to 1935. Any cases in which the diagnosis was somewhat questionable were not included. We wish to emphasize that the diagnosis of gout was quite conclusively established. Most of our cases were the ones in which certain fundamental studies in gout were made and published by Pratt,[3] McClure,[4] Folin, Berglund and Derick.[5] Thirty-nine (71%) of the 55 cases had tophi containing sodium urate crystals, universally accepted as pathognomonic of gout; the others had an unmistakable history of podagra, accepted by the above observers. Inasmuch as patients with gout usually die from other causes, we have autopsy studies in but 4 cases, and, fortuitously for this review, all of them had nephritis.

Analysis of Cases. In this series of 55 cases, there were 51 males, and 4 females (1 a negress). Among the males there were 2 Greeks, 1 negro and 1 Turk; the others were Anglo-Saxon. The average age for the series was 52.4 years, and most of the individuals had had gout for over 10 years. Hearty eating has always been associated with gout, but obesity did not seem to be any more common in these cases than in the general population between the ages of 40 and 60. However, nearly all of them had a history of alcoholism. Most of the cases were seen during an acute attack. There were no cases of leukemia to account for a high blood uric acid value, but there was 1 instance of polycythemia. One patient had had chronic lead poisoning. On a clinical basis the series has been divided into 2 groups, those with and those without nephritis.

Gout With Nephritis. Of the entire series of 55 cases, 17 (31%) had definite nephritis. The great majority of these individuals were thinner than those without demonstrable renal damage. Fourteen (82%) of these 17 had tophi and the average duration of gout for the group was 11 years. The evidence of nephritis consisted of persistent albuminuria and significant impairment of renal function, as shown by at least two of the following tests, phenolsulphonephthalein excretion, concentration tests, McClean urea index and azotemia (Table 1). In 5 patients the renal damage resulted in uremia and death. Decreased kidney function, due to obstruction in the lower urinary tract, was not a factor in any of the cases.

Albuminuria of moderate to marked degree was a constant finding in this group. Azotemia was present in the majority of the cases, the blood urea nitrogen ranging from 15 to 260 mg. per 100 cc. Hypertension was present in 13 of the 17 cases, an incidence considerably higher than in the non-nephritic group. The range

in blood pressure was from 110/65 to 240/140, with an average of 180/110. The blood uric acid in these cases was, for the most part, distinctly elevated.* Since the uric acid is usually elevated in chronic nephritis without gout, we have simply tabulated the uric acid values (Table 1), making no attempt to interpret them.

TABLE 1.—CASES OF GOUT WITH NEPHRITIS.

Case No.	Age.	Type of nephritis.	Albuminuria.*	Phenolsulphonephthalein, %.	Nitrogen retention, B.U.N.	Blood uric acid, mg.%.	Blood pressure.	Congestive heart failure.	Vascular disease.
1	59	Arteriosclerotic	+ + +		67	...	110/65	0	Severe.
2†	40	Arteriosclerotic and glomerular	+ + + + +	30–5	60	6.8	220/130	Slight	Moderate.
3†	46	Vascular	+ + + + +	5	260	...	220/120	Slight	Severe.
4	62	Vascular	+ + + +	25	21	5.6	170/120	Slight	Moderate.
5	43	Vascular	+ + + +	24	27	5.6	180/110	0	Slight.
6	55	Vascular	+ + + +	5	35	3.6	185/140	Slight	Severe.
7	58	Vascular	+ + +	12	35	3.3	140/70	0	Slight.
8	41	Vascular	+ + + + +	40	19	7.7	190/120	0	Moderate.
9†	61	Vascular	+ + + +	12	100	8.0	225/140	Slight	Moderate.
10	35	Vascular	+ + + +	30	41	8.3	220/140	0	Moderate.
11†	27	Chr. glomerular	+ + + +	5	215	6.7	120/80	Slight	Slight.
12†	46	Vascular	+ + + + +	5	260	...	200/120	0	Severe.
13	38	Vascular	+ + +	40	15	4.7	155/100	0	Slight.
14	35	Vascular	+ + +	30	32	6.8	190/120	0	Slight.
15	57	Vascular	+ + +	30	35	6.4	150/90	Moderate	Slight.
16	43	Chr. glomerular	+ + + + +	25	56	...	240/140		
17	43	Vascular	+ + +	42	30	3.5	135/95	0	Slight.

* Albumin: +, slightest possible trace; + +, very slight trace; + + +, slight trace; + + + +, trace; + + + + +, large trace.
† Died in Uremia. Phenolsulphonephthalein (I.M.), normal range, 45 to 65% in 2 hours.

The clinical type of nephritis in 15 of those 17 cases, as nearly as it could be determined, was vascular ("interstitial nephritis" or nephrosclerosis). The other 2 patients had chronic glomerular nephritis. Of the latter, 1 (Case 16) is most interesting in that, after a podagra history of 10 years' duration, he developed the nephrotic syndrome with rapid progression, within a year, to hypertension and renal failure. Death which occurred outside the hospital was due to uremia or to a cerebral vascular accident. The other patient was seen with subacute glomerular nephritis approximately 1 year before the onset of podagra (Case 11). He died in uremia 2 years later.

All of the cases in this group had clinical evidence of arteriosclerosis of moderate to marked degree. Retinal hemorrhages and white spots were present in at least 6 of the 17 cases. One patient

* There have been several modifications of the original Folin method of blood uric acid determination (1913), the range of normal changing with each improvement in technique. In addition, since the blood uric acid level alone does not make a diagnosis of gout, it is well not to interpret the figures too closely. To include the normal figures given in the various modified Folin tests carried out in this hospital, we have arbitrarily chosen 5 mg. per 100 cc. as the upper limit of normal blood uric acid.

had chronic lead poisoning, mentioned because of its possible etiologic association with both arteriosclerosis and gout.[6, 7]

As expected, with the nephritis and hypertension, the percentage of cases with congestive heart failure (41%) in this group was considerably higher than in those without nephritis. We were surprised to find that the average age of this group of patients with nephritis was 45, 10 years less than the average age of the patients without nephritis.

TABLE 2.—CASES OF GOUT WITHOUT NEPHRITIS.

Case No.	Age.	Albuminuria.*	Phenolsulphonephthalein, %	Nitrogen retention, B.U.N.	Blood uric acid, mg.%	Blood pressure.	Congestive heart failure.	Vascular disease.
1	48	0	...	...	...	130/90	0	0
2	66	++- ++++	80	19	5.0	165/95	0	Moderate.
3	59	0	61	...	6.8	190/120	Moderate.	Slight.
4	35	0	35	...	4.8	165/105	0	0
5	53	+++	...	...	2.4	115/90	0	0
6	43	0	50	28	4.9	130/90	0	0
7	45	+++	45	...	...	165/90	0	0
8	39	0	40	18	5.5	140/70	0	0
9	65	0	50	25	5.5	150/80	0	Slight.
10†	44	+	55	...	5.9	150/90	Severe.	Slight.
11	47	0	50	13	4.5	115/90	0	Slight.
12	54	0	...	10	3.0	130/90	0	Slight.
13	41	0	50	...	? 5.0	100/50	0	0
14†	62	++++	...	...	8.0	200/120	Moderate.	Moderate.
15	48	++++	...	...	6.0	125/80	0	Moderate.
16	56	0	...	...	...	145/90	Slight.	Moderate.
17	53	0	...	...	...	120/60	0	Slight.
18	57	0	...	...	1.0	135/80	0	0
19†	55	+++	55	...	5.7	148/80	Moderate.	Moderate.
20	70	+	40	...	...	180/90	0	Moderate.
21	68	+-+++	...	...	...	180/90	0	Moderate.
22	70	0	...	...	5.7	160/90	Severe.	Severe.
23	40	0	...	...	4.0-5.0	135/70	0	Slight.
24	65	0	45	11	4.7	215/120	0	Slight.
25	54	0	47	13	3.6	135/70	0	0
26	70	+++	...	15	...	180/80	0	Moderate.
27	58	0	...	...	6.3	160/90	0	Slight.
28	69	0	...	...	5.2	135/80	0	0
29†	69	+++	45	11	4.6	120/70	Severe.	Severe.
30	47	+	...	15	3.5	135/95	0	Slight.
31	40	0	45	9	4.2	130/90	0	Slight.
32	53	0	45	10	5.8	110/70	0	0
33	41	++- +++	50	15	3.9	125/90	0	0
34	64	0	50	8	4.4	210/105	0	Moderate.
35	66	0	50	20	5.2	210/120	Slight.	Moderate.
36	62	+++	45	...	...	185/100	Slight.	Severe.
37	57	+	50	14	6.4	215/105	0	Slight.
38	61	++	...	15	...	150/60	Slight.	Slight.

* Albumin: +, slightest possible trace; ++, very slight trace; +++, slight trace; ++++, trace.

† Albuminuria associated with cardiac failure. Phenolsulphonephthalein (I.M.): normal range, 45 to 65% in 2 hours.

Gout Without Nephritis. The average age for this group was 55 years. There was a slightly greater incidence of obesity in this group than in the other, but it was not unusual for this age period. Twenty of the 38 patients (53%) had tophi, and the average duration of gout in this group was 13 years, 2 years longer than in the cases with nephritis. As seen in Table 2, 16 of the cases had albuminuria of slight to moderate degree, but no other findings on which

to make a clinical diagnosis of nephritis. The albuminuria was due to cardiac failure in 4. However, in another case of severe congestive heart failure (Case 22) albuminuria was not observed in many examinations. During an attack of gout, albumin in the urine has been considered rather common, but it could be possibly attributed to this cause in only 8 cases (21%), in which we could find no other explanation.

Kidney function, as investigated by the tests already enumerated for the cases with nephritis, was essentially normal for this group. It was only slightly impaired in a few instances, not enough in any case, however, to warrant a clinical diagnosis of nephritis.[4] Although the uric acid excretion, before and after the use of various drugs, special diets and even the intravenous administration of uric acid was determined in most of the cases, we have considered it unnecessary to utilize these data, previously reported by others, as this would only lend further proof to the diagnosis of gout.

It has long been established that the blood uric acid need not be elevated even during an attack of gout. However, the blood uric acid was above 5 mg. per 100 cc. in 13 of the 38 cases of this group.

A comparison of the blood pressure in the two groups showed a striking difference. The average blood pressure was considerably lower in this non-nephritic group. Less than half—14—had hypertension (over 150 mm. Hg systolic and 95 mm. diastolic). In these 38 patients the blood pressure ranged from 100/50 to 215/120, averaging 165/90. As previously mentioned, these individuals showed considerably less arteriosclerosis, though they were 10 years older, and only 8 cases (21%) had congestive heart failure.

The fact that 16 cases with albuminuria and 14 with hypertension are included in a group of 38 cases under the heading "without nephritis" demands an added statement. The presence of albuminuria or hypertension alone does not make a diagnosis of nephritis. Although a significant degree of albuminuria and hypertension together was present in 6 of the 38 patients, as far as we were able to determine from the evidence available, there was no impairment of renal function to justify a diagnosis of nephritis in any of these cases.

Pathologic Anatomy. The pathologic descriptions of the kidney in gout in isolated cases in the literature for the most part have been those of chronic "interstitial" nephritis. The degree of contraction has been found to be so severe in some cases as to lead a few authors[8, 9] to describe this kidney as a "primary granular atrophy." Deposits of urates may occur in the interstitium of the kidney, usually in the medullary portion, best seen in the gross specimen, in addition to the interstitial nephritis. These deposits may be very extensive, as in a case recently described by Fahr,[10] but a survey of the literature shows that such instances are not the

rule in gout. Such deposits have not been given primary consideration, though Fahr would seem to place more significance upon them than do other writers. It is Umber's opinion[8] that "the urate deposits can exist in the gouty kidney without the manifestations of chronic nephritis, and they have in no way any serious connection with the renal disease." Many of the older clinicians supposed that the renal disease in gout predisposed to or caused kidney and bladder stones; we may presume that stones occurring coincidentally in a gouty patient might develop more rapidly, but nephrolithiasis is now supposed to have no necessary connection with gout, but to depend on bacterial and other local causes.[1] Finally, the most common form of uratic deposits in the kidney is the uric acid "infarct," composed of ammonium rather than sodium urate, occurring in infants. This condition has no association with gout.[10, 11, 12]

We are indebted to Dr. S. B. Wolbach for reviewing with us the histopathology of the kidneys of our 4 necropsied cases, descriptions of which follow:

Pathology of 4 Cases. CASE 1.—(Table 1.) The right kidney weighed 55 gm.; the weight of the left was not recorded, nor histologic examination made. The capsules stripped easily from a moderately granular surface of lighter color than usual. The left kidney contained a cyst, 2.5 cm. in diameter; the parenchyma of the right kidney contained a few smaller cysts. Microscopically, the glomeruli were essentially normal except in areas of fibrosis corresponding to a few moderately sclerosed arcuate arteries. There was only slight intimal thickening of the smaller arteries. The tubules for the most part were normal. Leukocytic infiltration was absent. The slight histologic changes were those of arteriosclerosis in a kidney weighing only 55 gm. It was concluded that the right kidney was hypoplastic.

CASE 2.—(Table 1.) The right kidney weighed 105 and the left 30 gm. The left was an anomalous mass of fibrous tissue with small cysts containing clear fluid; the right, a typical red granular kidney with a small adenoma in the upper pole. On section the cortex measured 3 to 6 mm. and was scarred; the glomeruli were irregular and indistinct. In the medulla were streaks of white crystallin material (uric acid crystals), most numerous in the boundary zone. This gave a fan-shaped and striped appearance. Microscopic study showed extensive diffuse fibrosis with atrophy of the remaining renal elements. Generally the glomeruli showed marked fibrosis of varying degree, the majority being reduced to acellular hyalinized cicatrices. However, the changes in a few were suggestive of an old glomerular nephritis. The large arteries showed marked concentric thickening of the intima, proliferative in type, with marked diminution of the lumen. The small arteries and arterioles showed thickening of their walls with hyalin changes associated with hypertension. The tubules were dilated or atrophied and separated through interstitial fibrosis. The process was predominantly that of arterial and arteriolar nephrosclerosis, possibly superimposed upon a healed glomerular nephritis.

CASE 3.—(Table 1.) Each kidney weighed 55 gm. The capsule stripped without difficulty from a finely granular, pallid surface. The cortex was thin and scarred. The smaller arteries appeared sclerosed. Microscopic study showed concentric thickening of the intima, proliferative in type, of the large arteries. The small arteries and arterioles showed marked hyalin degeneration and thickening of the walls. The glomeruli were markedly

reduced in number, being represented mostly by hyalinized fibrous tissue incorporated in areas of diffuse fibrosis. A few appeared essentially normal and hypertrophied. Others showed old subcapsular adhesions. Many of the tubules were atrophic or replaced by fibrous tissue; others were hypertrophied and distorted. The pathologic picture was that of a healed glomerular nephritis followed by arterial and arteriolar sclerosis with additional glomerular damage.

CASE 4.—(Table 1.) The left kidney weighed 185 and the right 160 gm. The capsule stripped with difficulty from a slightly nodular surface in which there were deep, irregular scars. The bloodvessels were moderately sclerosed; the cortex was slightly thinned. Microscopically, there were surprisingly few changes. The arterioles were essentially normal. An occasional small and medium-sized artery showed intimal thickening and hyalin degeneration with slight fibrosis of the corresponding glomeruli. Otherwise the glomeruli were not remarkable. There was no increase of connective tissue; no leukocytic infiltration. A few of the tubules showed slight epithelial degeneration. The residual changes, then, were those of slight arteriosclerosis. Moderate arteriolar sclerosis, however, not seen in the kidneys, was seen in sections of the pancreas and adrenals.

Discussion. For many years after the work of Garrod in 1848,[13] the theory that impaired renal function is the primary factor in the cause of gout largely dominated the viewpoint of both clinicians and pathologists. More recently, opponents to this theory[8, 14] have stated that functionally normal kidneys do occur in gout; pathologically, however, Moore[15] found normal kidneys in only 6 of 80 cases.

Before the development of modern renal function tests, a diagnosis of kidney disease was made chiefly from the presence of albuminuria and cylindruria alone, and obviously any statistics on such a basis are erroneous. By such criteria over half of our 55 cases had nephritis, but with our present methods, actually only 31% had enough renal impairment, as shown by ordinary clinical tests, to be termed nephritis.

We have included with our cases of nephritis 2 of the patients shown by McClure[4] to have, by more delicate tests, renal impairment, but insufficient at that time for a diagnosis of nephritis. However, further observation of these 2 cases has established a definite diagnosis of nephritis. Other cases reported in his series are included in our non-nephritic group. In his studies these showed only the slightest renal impairment; but unfortunately we do not have follow-up studies to determine if they too had nephritis. Contrary to McClure, we must conclude from the larger series now available for study, that impairment of renal function in gout, judged by the ordinary tests, is uncommon in the absence of nephritis. We also believe that albuminuria in gout, when not due to cardiac failure, is not as common as many have supposed in the absence of nephritis. This is in disagreement with Williamson,[16] who found albuminuria in 45% of his cases but diagnosed nephritis in only 6%. In 8000 cases of gout which Gemmel[17] claims to have observed, 10% had albuminuria and only 3 cases had definite evi-

dence of nephritis. These two are the only studies we have found in the literature, since the introduction of modern kidney function tests, giving an incidence of nephritis in gout. However, neither of these authors stated whether or not kidney function had been determined in their cases.

Associated with the supposed frequent occurrence of nephritis in gout, which has been regarded as "interstitial" or vascular in type, one would expect to find a large amount of generalized vascular disease as well as hypertension. However, the evidence in the literature on this point is contradictory. The viewpoint of the older writers is well expressed in an aphorism by Huchard,[18] that "the gout is to the arteries as the rheumatism is to the heart." The more recent concepts are as given by Aschoff,[19] that "genuine gout has nothing to do with arteriosclerosis," and by Allbutt,[1] that "regular gout and hypertension are not more than incidentally associated. . . . Arteriosclerosis, whether with high blood pressure or not, is a frequent but by no means obligatory concomitant of gout." From the high incidence of vascular disease (67%) and hypertension (54%) in our series we must agree with the opinion of the older clinicians. Mathieu, Collesson and Choltus[20] recently stressed the early development of vascular disease in gout.

For comparison, we have removed from our series the 3 known cases of glomerular nephritis in which the vascular disease and hypertension might be considered secondary to the renal disease and assumed that the remainder of the cases had at the beginning primary or essential hypertension simply occurring in a gouty subject, or even before the development of the gout in some cases. This showed a much higher incidence of vascular disease, hypertension and nephritis than in control groups of cases of similar ages. Furthermore, the incidence of the clinically manifested nephrosclerosis in these cases of gout is considerably greater than any control group of essential hypertension of similar ages.

Although data are not available regarding the percentage of clinical nephritis in essential hypertension, by the tests of renal function used in our cases of gout, the incidence would surely be much less than 25%. Fishberg[21] believes that the most important criterion that clinically significant renal impairment is present or definitely impends in essential hypertension is the appearance of papilledema and that this occurs in less than 10% of the patients. Likewise, compared to the general population of this age period, the frequency of vascular disease and hypertension is much higher in our series of cases of gout. Although the incidence of arteriosclerosis in the general population is difficult to establish accurately, Sydenstricker's extensive statistical studies[22] show clinical vascular disease in about 20 to 30% of individuals between 40 and 60 years. It is easier to determine the incidence of hypertension, and this, Alvarez and Stanley[23] found to be 12% in cross-section of the population in the same age period as our cases.

From the standpoint of nephritis alone, regardless of the type, everyone will agree that it does not occur in the non-gouty adult population in a per cent as high as we have observed in gouty patients (31%). Moreover, nephritis does not complicate other chronic diseases with any such frequency. For example, in chronic arthritis[24] and diabetes mellitus[25] nephritis is said to be of no greater frequency than in any group of normal individuals of the same age.* A high incidence has been given in pernicious anemia.[26, 27] An impairment of renal function in this disease, however, does not necessarily indicate nephritis, since kidney function may improve with the subsidence of the severity of the anemia.[28] Furthermore, the most recent observations[29] have shown less than 5% clinical nephritis in patients with pernicious anemia, even though it was predicted that liver therapy would produce kidney disease.[27] To reiterate, Fishberg states[21] that the complication of chronic arthritis, diabetes or pernicious anemia by "nephritis" is accidental.

In an attempt to explain the high incidence of vascular disease, hypertension and nephritis in our cases of gout, we have considered several of the more important factors believed to predispose to these conditions. Heredity is accepted as the most important, and it is the one stressed in most discussions of hypertension and of gout. Since only 2 of our cases gave a definite family history of gout, we agree with Williamson that the hereditary nature of true gout has been overemphasized. Garrod states[30] that there is an hereditary tendency toward "interstitial" nephritis in gout, but our observations do not substantiate this. There was a positive family history of vascular disease in 37% of our nephritis cases and 35% of those without nephritis. These figures are essentially the same found in control groups.[31, 32, 33] Opposed to this, a family history of vascular disease has been reported in 65 to 75% of the cases of primary hypertension.[31]

Alcohol at one time was thought to be[36] an important factor in the production of vascular disease. Inasmuch as alcohol has always been regarded as a companion of gout, and as nearly all of our cases were moderate to heavy drinkers, we felt this should be mentioned. It can be dismissed quickly with the statement that there is sufficient evidence in the literature that the etiologic significance of alcohol in vascular disease seems to have been disproved. Recent studies[34, 35, 36] have shown that alcohol in either small or large amounts plays no substantial part in the cause of arteriosclerosis, nor does it cause hypertension.[23] As a matter of fact, it has been Leary's observation that, as a class, persons suffering from alcoholism appear to show a lesser degree of atherosclerosis than their ages would justify.[37]

* Since writing this paper, Joslin (The Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, p. 164, 1935) has stated that the incidence of chronic vascular nephritis is somewhat higher in diabetic than in non-diabetic patients.

Obesity and diabetes mellitus are other factors included in most treatises on vascular disease and hypertension. There were no instances of diabetes in our series. Obesity, though it may not necessarily be a cause of high blood pressure, is a frequent concomitant of essential hypertension.[38] In the entire series there was no greater frequency of obesity than one finds in normal individuals of this age; however, the patients without nephritis showed slightly more obesity than the nephritic cases which had the more vascular disease. No one of the other numerous factors usually given in consideration of vascular disease and hypertension would account for the high incidence of these conditions in our cases. It seems, therefore, that we must attribute the unusual amount of vascular disease and increased blood pressure to some other factor, possibly to the gout itself.

With the exception of 2 cases of glomerular nephritis diagnosed clinically and another one diagnosed pathologically, the remainder of the cases of nephritis, as far as we could determine clinically, were of the vascular type. There was only 1 patient, a case of subacute glomerular nephritis, in which we were certain that the nephritis antedated the gout (Case 11, Table 1). In another patient the glomerular nephritis and nephrotic syndrome, which evidently developed years after the onset of podagra, was probably unrelated to his gout.

Pathologically, most of the various changes that have been described for the kidney in gout are represented by the 4 cases that came to necropsy. These were arterial and arteriolar sclerosis, with and without uratic deposits in the interstitium, chronic glomerular nephritis with the usual secondary vascular changes in the kidney and arteriosclerosis of the medium-sized arteries in the absence of significant changes in the arterioles. This last condition in 1 case was hardly more than one would expect in an individual of this age; however, clinically there was evidence of at least a moderate degree of nephritis. Although it seems necessary to consider some unknown factor to account for the high incidence of vascular disease and nephritis in our cases, it appears evident that clinically and pathologically the underlying lesion in the kidney was predominantly vascular. The glomerular nephritis does not seem related necessarily to the gout, and its occurrence was probably not greater than would be expected in any collection of cases of chronic nephritis in the broad sense.

Summary. In a study of 55 cases of true gout, 17 (31%) had clinical nephritis substantiated by commonly used tests for renal function. It was of the vascular type in 15 and glomerular in 2. One of the latter had the nephrotic syndrome. Five died in uremia. Of 4 cases necropsied, 3 had predominantly vascular nephritis and 1 had glomerular nephritis. The average age of the cases with nephritis was 10 years less than that of the non-nephritic group.

Of the remaining 38 cases without nephritis, 16 had albuminuria; in 4 of these it was definitely cardiac in origin. In this group renal function was very slightly impaired in 1 case and questionably so in 3, but not enough for a diagnosis of nephritis. Compared to certain control groups, the incidence of hypertension in the 55 cases (54%) and of vascular disease (67%) was high.

Conclusions. 1. An incidence of 31% of chronic nephritis in 55 cases of true gout is unusually high when compared to other chronic diseases, as essential hypertension, chronic arthritis, diabetes mellitus and pernicious anemia.

2. From our clinical and pathologic studies the type of nephritis in gout is predominantly vascular, although glomerular nephritis does occur, possibly unrelated to the gout. Assuming that in our cases the vascular disease was generalized, from some cause which we could not determine, it progressed into clinical nephritis at an earlier age and in greater frequency than occurs in non-gouty subjects with or without hypertension.

3. Vascular disease and hypertension are more frequent in patients with gout than in non-gouty individuals of the same age. Heredity, alcoholism and obesity appeared to play no part in the vascular disease or hypertension.

4. From our study of 38 gouty subjects without nephritis, contrary to the opinion of others, we believe that kidney function is rarely significantly impaired in the absence of nephritis. Albuminuria in gout, when unrelated to cardiac failure, is not as common as has been believed, 21% in our series, unless nephritis is present.

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LIPOID PNEUMONIA AND CONDITIONS THAT MAY FAVOR ITS OCCURRENCE.

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In the past few years several reports of so-called "lipoid" or "oil aspiration" pneumonia have appeared, chiefly in American pediatric and pathologic literature. It has previously been pointed out that a localized, proliferative and relatively benign type of pulmonary consolidation associated with the aspiration of lipoid material was sufficiently distinctive to be recognized as a pathologic entity; only, however, since Laughlen's[1] observations has the condition been diagnosed clinically. As the experimental and clinical studies leading to its establishment as an entity have been adequately discussed by Pinkerton,[2] Goodwin,[3] and Ikeda,[4] review of other cases will not be included. The following 3 cases, all in children under 2 years of age, have been observed within the past 7 months on the service of the Children's Clinic of the New York Hospital.

Case Reports. CASE 1 (N. Y. H. 80963).—E. G., an 11-month-old male infant of Polish Hebrew parentage, was admitted to the hospital with the complaint of having had "phlegm on the chest" for 10 months and of never having developed normally. He had been put into a plaster cast within a few days after birth to correct a congenitally dislocated hip; for the first 2 months of life, therefore, he was practically immobile. The sequence of events during this period is not entirely clear but supposedly the baby developed a mild upper respiratory infection by the second week of life and from this he did not recover. By the fourth week he had a cough, constantly drooled large quantities of mucus which collected in the pharynx, vomited often and gained weight very slowly. He received either 20 drops of viosterol or 2 tablespoonfuls of cod liver oil daily, and, by the second month, in an effort to combat what seemed to be an almost continuous respiratory infection, he received albolene nose drops daily. The use of these drops was not discontinued until after hospitalization.

The child's condition remained relatively stationary for 7 months, that is, there was a more or less constant cough, accompanied by cyanosis during severe attacks, and associated with an excess amount of mucus in the throat. Vomiting was frequent, often nasal in type, with large amounts of mucus in the vomitus. He was subject to severe head colds about twice a month, episodes accompanied by fever and a profuse nasal discharge; from these he scarcely recovered before another infection supervened. During the summer months spent at the seashore he improved slightly and colds were less frequent following adenoidectomy in September, 1934. At this time the only Roentgen ray which was taken during his 10 months of illness was secured. It has been impossible to locate the film but the parents were told that he had "congested lungs" and an enlarged thymus; the child received Roentgen ray treatments for the latter condition. The infant had never been able to hold his head up or to sit alone. He did not talk. He recognized his parents and they felt that he also responded to external stimuli, such as the radio, but he had never played actively with toys. Dentition had been normal.

Physical examination in the Outpatient Department 10 days before hospital admission revealed mucus in the upper respiratory passages and increased tactile fremitus at both bases, but there were no changes in percussion note or adventitial sounds in the chest. In the 3 days before admission he developed a fever, vomited repeatedly, and seemed very weak. He was at this time thin, pale and listless, an infant who, despite his 10 months, looked no more than 3 months of age. Body measurements confirmed the impression of a marked physical underdevelopment. Due to the physical retardation it was difficult to evaluate the mental status. He grasped for objects if interested, recognized his parents, responded at times to spoken commands. He cried very feebly and made almost no voluntary movements, the extremities lying flaccidly wherever they were put. On admission his temperature was 37.8° C., respirations, 45, and pulse rate, 140. He presented the signs of a bilateral acute catarrhal otitis media and mild rhinopharyngitis. The mouth was held open most of the time, an excessive amount of saliva running out over the chin and almost completely obscuring the view of the pharynx. The gag reflex was very sluggish. Examination of the lungs revealed an impairment of the percussion note on the right, anteriorly over the upper lobe, in the axilla and over the interscapular region. Breath sounds were very harsh throughout so that a superimposed pulmonary infection was postulated. The liver was palpable at the costal margin. Upon neurologic examination the reflexes were sluggish; marked hypotonicity of all tendons and musculature was present. There was a slight enlargement of lymph nodes (posterior cervical axillary and inguinal). There was no clubbing of the fingers and no other abnormalities. The red

blood cell count was 4,190,000 cells per c.mm.; white cell count 10,000 of which 42% were adult neutrophils, 15% immature, 38% lymphocytes, 2% monocytes and 3% eosinophils. A Mantoux test with 1 mg. of tuberculin was negative. Smear from the throat revealed many streptococci and staphylococci and M. catarrhalis, beta hemolytic streptococci, and B. coli communior were grown in culture. Repeated blood cultures were sterile and examinations revealed no abnormalities in chemical constituents of the blood. Roentgenograms showed the typical picture of a lipoid pneumonia as emphasized by Goodwin[3] with a superimposed bronchopneumonia on the left. The densities in the right hilar field remained unchanged during his illness, the other shadows changing at each examination.

Three days after admission the child's temperature rose to 39° C., and his respirations to about 60, the signs of a pneumonic process became more prominent, and a purulent otitis media, staphylococcic in origin, developed on the left. After the ninth day he was markedly worse; temperature varying from 39° to 41° C., the number of white blood cells falling steadily, pulse ranging from 130 to 180 and of very poor quality, the signs of consolidation increasing. Despite repeated transfusions, oxygen, and the usual cardiac stimulants, the child died 14 days after entry to the hospital, being practically moribund for the last 72 hours.

Autopsy (No. 7949). (Dr. Angevine, 2 hours after death.) The subject was poorly developed. The lungs were a mottled yellow-brown color except over the posterior part where there was considerable congestion. The pleura over the right upper lobe was thick, and firmly adherent to the parietal pleura. The right upper lobe was firm and cut with increased resistance. The remaining lobes of both lungs were firm and subcrepitant throughout because of the firm yellow-brown nodular areas that measured up to 5 mm. The cut surface was greasy and droplets adhered to the knife; they stained red with Sudan III. Small beads of purulent exudate were expressed from the terminal bronchi. The bronchial lymph nodes were enlarged about twice the normal size. The cut surface was a yellow-gray color and had the appearance of fat.

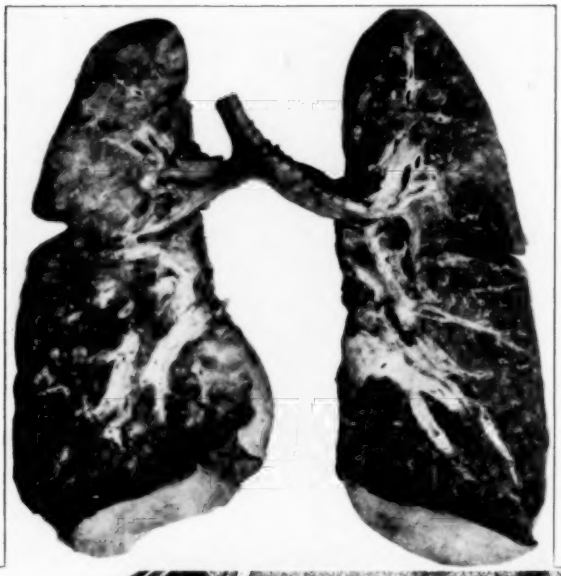
Microscopic Description of Lungs. A section through most of the right lung (Fig. 2) shows a lobular pneumonia with discrete nodules at the periphery of the lung becoming more confluent toward the hilus. Under higher magnification there are many large mononuclear cells containing fat droplets; they occur in groups with a lobular distribution and are associated with an increase of fibrous connective tissue. A cuboidal type of epithelium (Fig. 3) lines the alveoli and in many areas there is an acute inflammatory lesion composed largely of neutrophils. There are numerous large multinucleated giant cells (Fig. 5) containing fat droplets in the cytoplasm, and in several alveoli there are clumps of irregularly shaped masses of bluish staining material. Adjacent lymph nodes also contain many large mononuclear fat laden cells. In a frozen section stained for fat, most of the large extracellular droplets as well as the intracellular fat are sudanophilic. About one-fourth of the fat stains selectively with osmic acid.

Bacteriology. Pfeiffer bacilli were recovered from the heart blood; Pfeiffer bacilli and a non-hemolytic streptococcus from the lung.

Anatomic Diagnosis. Lipoid pneumonia of both lungs with consolidation of the right upper lobe; Zenker's degeneration of skeletal muscle; atrophic thymus.

Case 2 (N. Y. H. 88565).—The child was a colored infant born prematurely in the seventh month of pregnancy. Birth history was unremarkable and there were no neonatal disturbances. At the age of 4 months he had rickets and 1 to 3 teaspoons of cod liver oil were administered from this time until hospital admission at the age of 8 months. The child had never sat alone, had had frequent spasmodic attacks of muscular twitchings

1



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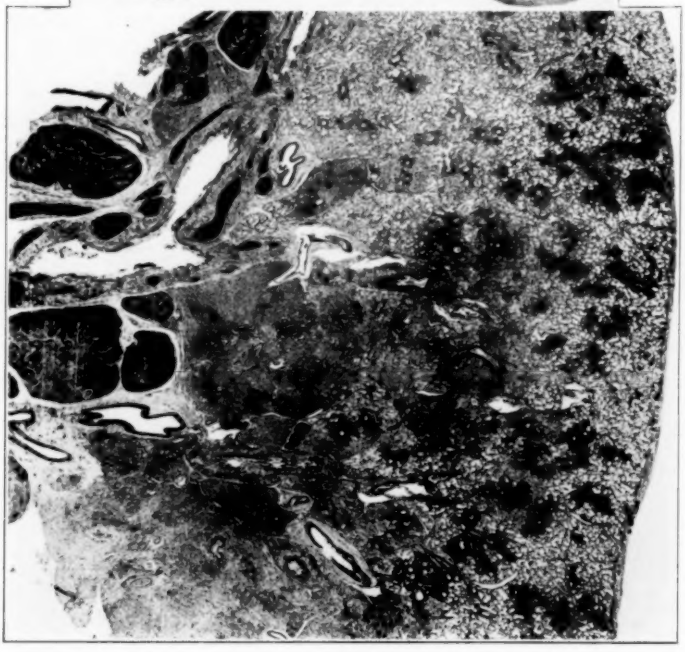

FIG. 1.—Autopsy 8035. A median section of the posterior halves of both lungs. The lipoid pneumonia involves the upper and a part of the lower lobe of the right lung.

FIG. 2.—Autopsy 7949. A section of the left lung to show the diffuse and nodular bronchopneumonia. Note the enlarged peribronchial lymph nodes. (× 4.)

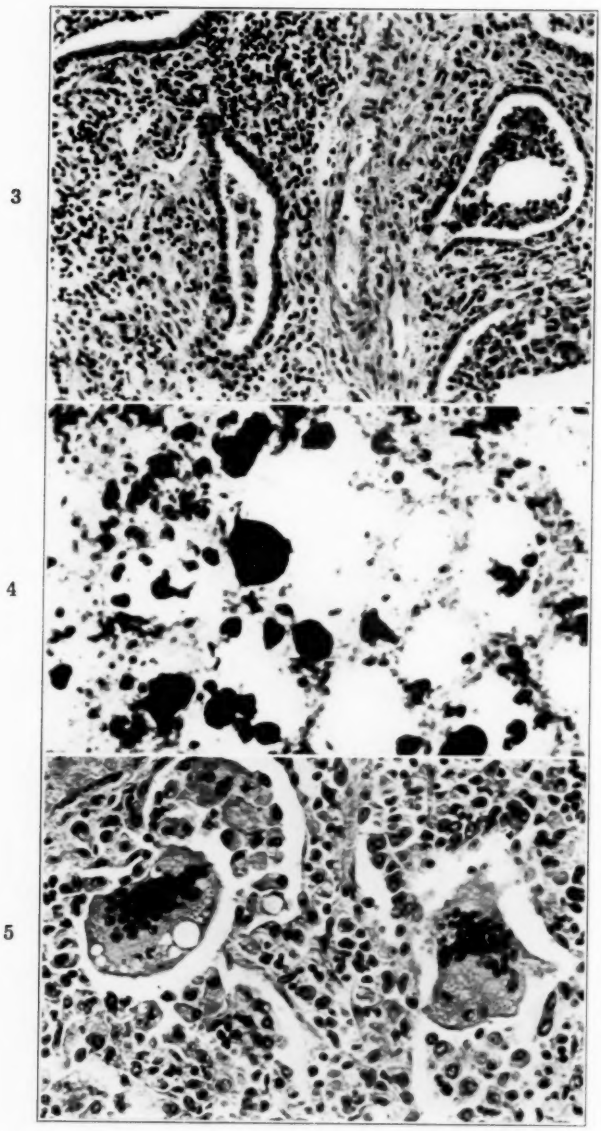

Fig. 3.—Autopsy 7949. A section to show the cuboidal epithelium lining the alveoli, the increase in fibrous connective tissue and the large numbers of neutrophils. (× 180.)

Fig. 4.—Autopsy 8171. Frozen section stained with Sudan III. The black droplets represent mineral oil. (× 150.)

Fig. 5.—Autopsy 7949. To illustrate large foreign body giant cells containing oil droplets. (× 390.)

and movements of the extremities and he had never been a "bright baby." Dentition had been normal. His terminal illness began 3 days before admission when he had a fever, refused to eat, had been restless and finally developed labored respirations and vomited.

Upon admission the child was acutely ill, semicomatose, with a fever of 41° C., respirations 38, pulse 120. He was extremely well developed, but poorly nourished. Rachitic stigmata were present in the head and chest. There was definite evidence both on physical examination and by fluoroscopy of a pneumonic process in the upper lobe of the right lung, but this was not verified by any marked area of consolidation in the Roentgen ray films taken the next day. He had an acute pharyngitis and a bilateral catarrhal otitis media. The spleen and liver were enlarged and there was a small umbilical hernia. Interest was focussed chiefly upon the neurologic findings, for, in addition to a tense and bulging anterior fontanelle, he had a markedly stiff neck and a positive Brudzinski. All deep reflexes were hyperactive. Babinski, Oppenheimer, Gordon, Chvostek responses were negative. He was subject to intermittent spells of purposeless movements of the upper extremities, facial grimacing and twitchings. The arms were often thrown out violently with the hands, at times, in typical carpopedal spasms. Movements in the lower limbs were much less marked, though definite spasms were observed in small muscle groups. The hypertrophy of the skeletal muscles in the limbs gave the child the appearance of a miniature professional wrestler, the clinical picture simulating that described recently by de Lange.[5] The head was held, for the most part, sharply turned to the right. Positive Brudzinski and Babinski signs were later elicited inconstantly; the neck and labyrinthine reflexes of Magnus and de Kleyne, spasticity and clonus in the lower jaw, also being observed. The pharyngeal reflex was not very active. Eye grounds were normal. Lumbar tap released a clear fluid under no increase of pressure. The child did very poorly, his temperature and respiratory rate increasing steadily, and he died 54 hours after admission. There were no unusual findings in the laboratory studies.

Autopsy (No. 8035). (Dr. Angevine, 35 hours after death.) The subject was a well developed male infant that weighed 6500 gm. The findings of greatest interest were those in the brain and lungs.

There was a thickening of the pia arachnoid, especially in the interpeduncular region. The walls of the internal carotid arteries were slightly thickened and there was a moderate degree of internal hydrocephalus. The choroid plexus in both lateral ventricles was somewhat atrophic. The third ventricle, aqueduct of Sylvius and the fourth ventricle were all slightly dilated. The optic thalamus on both sides was atrophic. Sections from the brain and spinal cord show a definite thickening of the meninges with an increase of fibrous connective tissue but few cells, mostly lymphocytes.

The lungs were salmon pink in color except over the posterior parts where they were congested. The right upper lobe was firm and through the pleura several small yellow lobular areas that measured up to 3 mm. were seen. The cut surface (Fig. 1) showed almost the entire upper and a small part of the lower lobe to be yellow-gray in color; the larger lobular areas were for the most part confluent except toward the periphery where they were circumscribed. A definite and unmistakable odor of fish oil was readily detected. The lymph nodes were slightly enlarged.

Microscopic Description of Lungs. In a section from the upper lobe of the right lung stained with hematoxylin-eosin there is a rather diffuse exudate composed largely of neutrophils together with mononuclears and erythrocytes. There is a slight increase in fibrous connective tissue and a few large multinucleated giant cells containing clear droplets. The bronchial epithelium is hyperplastic in one area. There are numerous large empty spaces, previously occupied by fat droplets. The alveoli are lined by a cuboidal epithelium in several places. In a frozen section many large

droplets take the Sudan III stain. In addition there are many cells containing small discrete orange stained droplets in the cytoplasm. In an osmic acid preparation there is about an equal amount of black staining material varying considerably in size and shape.

Anatomic Diagnosis.—Lipoid pneumonia of right lung; internal hydrocephalus; hemorrhagic pachymeningitis externa; Zenker's degeneration of skeletal muscle.

CASE 3 (N. Y. H. 79114).—A Jewish infant, 19 months of age, had developed normally up to the age of 6 months, after which she began slowly to degenerate mentally with a progressive hyperacusis, lethargy, and failure to note objects. There was no familial story of degenerative disease nor had the patient previously been ill. Her course was that of the typical case of amaurotic family idiocy, complicated 6 months before death by fever attributable to erysipelas, pyelitis, stomatitis and an upper respiratory infection. The pyelitis and stomatitis cleared rapidly but the skin infection was fairly prolonged. During the 10 months of her illness no symptoms of pulmonary disease were noted until about 6 months before death. There was then an area of dullness to percussion in the interscapular region, more marked on the right than on the left, and not varying markedly between examinations. There was also an increase in the intensity of the breath sounds in this region with an occasional râle. She ran an irregular fever during the last few months of life. A diagnosis of lipoid pneumonia was made and confirmed by repeated fluoroscopic examinations. She had been given 15 cc. of mineral oil and 10 drops of viosterol during most of the time she was in the hospital, and there was considerable difficulty in feeding her. Convulsive seizures were intermittent for many months before her death.

Autopsy (No. 8171). (Dr. R. J. Parsons; 2 hours after death.) The brain was large, heavy and firm; it weighed 1660 gm. The convolutions were larger than normal. The entire cerebellum, the pons and optic nerves were atrophic and small in comparison to the large hemispheres. The gray matter of the basal ganglia and cortex was unusually pale and firm. Sections from several areas of the brain and spinal cord are very similar. The nerve cells are much enlarged, rounded, vacuolated, and the Nissl substance is finely broken up. Material stained with Sudan III shows many large phagocytic cells filled with sudanophilic material.

Both lungs were of normal size. There were many definite discrete or confluent yellow nodules over the posterior half of the right lung that measured up to 1 cm. They were most conspicuous over the upper lobe and toward the hilus. On the cut surface these nodules were rather bright yellow in color, firm and slightly elevated above the surrounding normal lung tissue. The bronchial lymph nodes were enlarged to about twice their usual size.

Microscopic Description of Lungs. In many areas there is a quite definite fibrous thickening of the interalveolar septa with obliteration of the alveolar structure. Many alveoli are completely, and others partially, filled with large mononuclear phagocytes, the cytoplasm of which is filled with large clear vacuoles. A few neutrophils are seen in the capillaries of the interalveolar septa and a small number are free in the alveolar spaces. A Sudan III preparation (Fig. 4) shows abundant sudanophilic material varying from small intracellular droplets to large globules and amorphous masses that fill entire alveoli. An osmic preparation shows only one small free globule that stains black.

Other findings were an increase of fat in the lymphoid follicles of the spleen, about the central vein and in the Kupffer cells of the liver.

Bacteriology. Hemolytic staphylococcus aureus, non-hemolytic streptococcus and Bacillus coli communis were recovered from the lung.

Anatomic Diagnosis. Gliosis of brain and spinal cord (Tay-Sachs disease); lipoid pneumonia.

Summary. Three cases of lipoid pneumonia in infants under 2 years of age are described. Two occurred in children with extensive pathologic lesions of the central nervous system and one in a debilitated child who was restrained in a plaster cast because of a congenital dislocation of the hip. Clinical diagnoses were made in 2 instances on the basis of history with the physical findings and characteristic roentgenologic picture described by Goodwin.[3] In 2 cases the cause was apparently the administration of mineral oil together with viosterol. The other case was due to codliver oil alone.

The fresh lungs all presented a somewhat similar and characteristic picture except for the amount of lung involved. They all showed yellow-brown, rather firm nodules readily seen through the pleura. The right lung and especially the upper lobe was most extensively involved in each instance. The diagnosis was made on the gross specimen in all cases and additional confirmatory evidence was obtained by the microscopic examination of scrapings from the fresh cut surface of the lungs for fat droplets. In 1 instance the sense of smell was of great aid. Microscopically the 3 cases showed a somewhat similar process, consisting of varying degrees of fibrosis and an infiltration into the alveoli of large mononuclear leukocytes filled with fat; in addition to this in 2 instances there was acute bronchopneumonia. In 2 cases cuboidal epithelium lining the alveoli was conspicuous and numerous large multinucleated foreign body giant cells containing fat droplets were present. Although the diagnosis can be readily made with an hematoxylin and eosin stain, it is highly desirable to make Sudan III and osmic acid preparation as an aid in determining the nature of the aspirated fat.

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THE INTRANASAL APPLICATION OF INSULIN, EXPERIMENTAL AND CLINICAL EXPERIENCES.*

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Since the discovery of insulin investigators have attempted to introduce it into the body by various methods. Woodyatt,[1] in

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1922, says, "Experiments were conducted with oral, rectal, vaginal, intranasal, intravenous, and subcutaneous administrations. Inunctions were also tried. Many variations were attempted in connection with each. Positive effects were obtained with subcutaneous and intravenous injections, very weak, doubtful or frankly negative results with the others." Up to the present time intravenous and subcutaneous administrations have been employed to the exclusion of all other methods.

Telfer,[2] in 1923, reported that insulin could be introduced into the blood stream by means of inunction. Harrison,[3] in 1926, repeated this work and found that the inunction of insulin was useless even in very large doses. Peskind, Rogoff and Stewart,[4] in 1924, found that insulin when injected per rectum into rabbits was absorbed and produced lowering of the blood sugar; in dogs, negative results were obtained. Heubner, de Jongh and Laquer,[5] in 1924, describe the lowering of blood sugar in diabetics by inhalation of insulin. Fisher,[6] in 1924, found some absorption of insulin by the intestine, vagina and scrotal sac. Gänsslen,[7] in 1925, described lowering of the blood sugar in diabetics by inhalation of an insulin spray. Miller,[8] in 1926, reported that insulin given in absolute alcohol or 95 per cent alcohol solution in keratinized capsules, lowered the blood sugar of diabetic patients. Stephan,[9] in 1929, described lowering of blood sugar following the administration of insulin by mouth. This work was not confirmed by Wahncau and Bertram[10] or by Bertram, Horwitz and Wahncau.[11] Bollman and Mann,[12] working with intestinal catheters and with ileac loops, found that large amounts of insulin might be instilled into the duodenum, jejunum, or ileum without any appreciable effect on the blood sugar of normal dogs. Similar results were found with administration into the ileac loop.

A summary of these results bears out the initial statement of Woodyatt that with methods other than subcutaneous or intravenous injection "very weak, doubtful or frankly negative results" have been obtained.

Recently we have repeated some of these experiments with variations, and in the course of our work, studied the problem of intranasal absorption. We have obtained undoubted evidence of the activity of insulin, either when sprayed or when instilled into the nostrils in normal rabbits, normal dogs and in diabetic patients under certain conditions.

The preliminary experiments indicated that the instillation or insufflation of insulin in the nose produced either frankly negative or doubtful results. We studied next various solutions which might possibly increase absorption through the mucous membrane. Finding several solutions which apparently had this effect, we chose first ethylene glycol as a medium. We have mixed equal quantities of ethylene glycol and insulin, using a highly concentrated solution

of insulin containing 1000 units per cc. The solutions employed for instillation contained 500 units per cc. With such a solution 0.1 cc. contains 50 units and 0.2 cc., 100 units of insulin.

The following are a few typical protocols on rabbits and dogs:

Date, 1935.	Animal.	Time.	Blood sugar, mg.
Mar. 13	Rabbit No. 1	8.50 A.M.	247.0
		8.55 A.M.	0.2 cc. insulin-ethylene glycol-mixture (100 units) intranasally.
		10.28 A.M.	177.0
		11.47 A.M.	149.0
Mar. 15	Rabbit No. 2	9.05 A.M.	105.5
		9.08 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
		10.40 A.M.	62.5
		12.40 A.M.	55.2
Mar. 20	Dog	9.50 A.M.	96.0
		9.55 A.M.	0.4 cc. insulin-ethylene glycol mixture (200 units) intranasally.
		10.50 A.M.	58.8
		11.45 A.M.	58.3
		12.45 P.M.	44.2

The effects of this solution when applied intranasally in diabetic patients were next studied. All of the patients studied had been under observation in the diabetic clinic for varying periods of time. On the day when the test was carried out both breakfast and the morning dose of insulin were omitted. In a few instances the evening dose before the day of the test was also omitted. The results are seen in the following table:

Case Reports. CASE 1.—Female, aged 70, first seen, January 30, 1935, with a fasting blood sugar of 233 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 150, protein 60, fat 90. Insulin dosage in units, 20 – 5 – 20, a total of 45 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 18	7.30 A.M.	150
	8.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	9.15 A.M.	149
	10.15 A.M.	122
	11.15 A.M.	83
	12.15 P.M.	110

CASE 2.—(Same patient as Case 1.)

Date, 1935.	Time.	Blood sugar, mg.
Mar. 19	7.30 A.M.	135
	8.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	9.15 A.M.	87
	10.15 A.M.	94
	10.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	11.15 A.M.	69
	11.15 A.M.	Slight reaction.
	11.30 A.M.	More marked reaction.
	11.40 A.M.	Orange juice.
	12.15 P.M.	115

CASE 3.—Male, aged 23, first seen, October 30, 1933, with a fasting blood sugar of 571 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 100, protein 100, fat 150. Insulin dosage in units, 11 – 0 – 9, a total of 20 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 21	8.00 A.M.	225
	8.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	9.50 A.M.	197
	10.50 A.M.	172
	11.50 A.M.	148
	12.00 NOON	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	1.00 P.M.	137
	2.00 P.M.	116
Mar. 22	7.00 A.M.	189
	3.00 P.M.	242

Case 4.—Female, aged 24, first seen, March 21, 1935, with a fasting blood sugar of 256 mg. per 100 cc. The patient had followed no strict diet and had taken no insulin regularly before test.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 21	8.00 A.M.	256
	8.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	9.50 A.M.	154
	10.50 A.M.	125
	11.50 A.M.	115
Mar. 22	7.00 A.M.	254

Case 5.—Female, aged 64, first seen, March 28, 1935, with a fasting blood sugar of 217 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 75, protein 50, fat 75. Insulin dosage in units, 10 – 5 – 10, a total of 25 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 29	8.30 A.M.	188
	9.30 A.M.	180
	9.40 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	10.30 A.M.	144
	11.30 A.M.	142
Mar. 20	7.00 A.M.	167

CASE 6.—Female, aged 47, first seen, April 28, 1928, with a fasting blood sugar of 323 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 50, protein 75, fat 100. Insulin dosage in units, 25 – 15 – 20, a total of 60 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 30	12.15 P.M.	158
	12.20 P.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	1.15 P.M.	106
	2.15 P.M.	65
	3.15 P.M.	66

CASE 7.—Male, aged 44, first seen, April 3, 1935, with a fasting blood sugar of 286 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 50, protein 100, fat 150. Insulin dosage in units, 10 – 0 – 10, a total of 20 units per day.

Date, 1935.	Time.	Blood sugar, mg.
April 3	10.45 A.M.	286
	10.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	11.45 A.M.	112
	12.45 P.M.	67
	1.45 P.M.	73
April 4	7.00 A.M.	132

We next made observations employing trimethylene glycol instead of ethylene glycol. These solutions were prepared so that 0.1 cc. of the solution contained 75 units. The pH of the solution employed was 2.5. These solutions were apparently more active than those made with ethylene glycol.

CASE 8.—Female, aged 75, first seen, October 11, 1934, with a fasting blood sugar of 322 mg. per 100 cc. The patient had followed no strict diet before the test. Insulin dosage in units, 14 – 0 – 12, a total of 26 units per day.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	206
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	157
	2d hour	146
	3d hour	132

CASE 9.—Male, aged 34, first seen, June 15, 1935, with a fasting blood sugar of 238 mg. per 100 cc. The patient had followed no strict diet and had taken no insulin regularly before the test.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	203
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	222
	2d hour	198
	3d hour	189

CASE 10.—Male, aged 54, first seen, May 1, 1935, with a fasting blood sugar of 335 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 150, protein 75, fat 100. Insulin dosage in units, 20 – 10 – 20, a total of 50 units per day.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	310
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	224
	2d hour	165
	3d hour	158

CASE 11.—Male, aged 66, first seen, June 26, 1935, with a fasting blood sugar of 213 mg. per 100 cc. At the time of the test the patient was on a

diet of carbohydrate 100, protein 75, fat 50. Insulin dosage in units, 15 – 10 – 15, a total of 40 units per day.

Date, 1935.	Time.	Blood sugar, mg.
July 14	Fasting	240
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	184
	2d hour	156
	3d hour	184
July 15	7.00 A.M.	211

Discussion and Summary. The above tables, which are examples of a larger group of similar observations, show that insulin in ethylene glycol and in trimethylene glycol when either dropped or sprayed into the nasal mucous membrane produces an unquestioned and marked fall in blood sugar in normal rabbits, normal dogs, and in diabetic patients. The dosage employed by this intranasal method is considerably greater than that necessary in subcutaneous injection.

Two impressions that we gain may be of some interest: First, in patients who prove later to be mild diabetics, the blood sugar falls very rapidly following intranasal application even when the blood sugar values are very high. Our second impression is that it is relatively difficult to produce insulin shock. While it is not difficult to lower the blood sugar from a high value to a range of 140 to 160, it is more difficult to lower the blood sugar below this level.

We have treated 15 patients in the hospital over periods of time varying from 2 weeks to 2 months and have been able to keep them relatively sugar free by the intranasal method. Whether this method of administration is practical in the treatment of diabetic patients further observations alone can determine. The treatment may prove too expensive to be practical and we may also discover that the variations in absorption in different patients at different times are too great to make this method of administration either practical or desirable. The fact that insulin under certain conditions can be absorbed from mucous membranes may, however, be of more than academic interest. Obviously the insulin molecule is not too large to pass through the intact mucous membrane. The action of the solutions employed in increasing absorption is not understood beyond the statement that they increase permeability. At present we do not believe that these observations establish either the desirability or the reliability of intranasal administration. They do, however, prove that intranasal absorption is possible.

We are under obligations to Eli Lilly and Company for the insulin used in these observations.

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THE EFFECT OF GASTRIC JUICE, BILE, TRYPSIN AND PANCREATIN ON INSULIN: THE PREVENTION OF THE DIGESTION OF INSULIN WITH ALCOHOL.

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(From the Medical Clinic of the Peter Bent Brigham Hospital, with the approval of Dr. H. A. Christian.)

Various attempts to make the oral administration of insulin effective have been practically unsuccessful. The reasons for these failures have been obscure. However, it appears either that insulin is destroyed or inactivated by gastro-intestinal enzymes or that the intestinal mucosa is impermeable to insulin, possibly because of its high molecular weight, which Sjörgen and Svedberg[1] found to be 35,100.

The purpose of this study was to investigate why the oral administration of insulin appears to be ineffective by determining the effect of gastric juice, trypsin, pancreatin and bile on insulin and to attempt to protect insulin, especially with alcohol, from being digested by these enzymes. This paper reports the results obtained in 116 experiments.

That insulin is destroyed by pancreatic juice was determined by Banting and Best.[2] This observation was confirmed by Scott[3] and by Dudley,[4] who showed, in addition to the inactivation of insulin by trypsin, that pepsin produced the same destructive effect. That the intestinal mucosa is impervious to insulin was suggested by the work of Bollman and Mann.[5]

Nevertheless there have been some studies which suggested that insulin may be protected by various substances and absorbed from the alimentary tract. Fisher and Noble[6] were able to recover insulin from the urine, when administered by mouth. Winter,[7] Miller[8] and Harrison[9] gave insulin in alcohol orally and caused a reduction in the blood sugar. However, Blatherwick, Maxwell and Long[10] could not confirm these results. Murlin and Hawley[11] obtained considerable absorption of insulin protected by blood serum when given by stomach tube to depancreatized dogs. Lasch and Brugel[12] caused a decrease in blood sugar in man and in animals giving insulin in saponin and normal saline. Hamburger[13] found that insulin dissolved in Ringer's solution is absorbed from the frog's intestine. Walton and Bassett[14] introduced insulin diluted with saline into the intestines of normal dogs with Thierry loops and produced typical hypoglycemia. Harned and Nash[15] described a preparation of antitrypsin which, when added to insulin and introduced into the duodenum, resulted in a considerable drop in the blood sugar. Fisher and Scott[16] observed no marked decrease in the physiologic activity of insulin after incubation at 37° C. with pepsin at pH 4. Jensen and Evans[17] suggested that the inactivation of insulin is connected in some way with hydrolysis of the protein.

Material. The gastric juice which was used was obtained by aspirating the fasting or non-fasting contents from patients with peptic ulcer, carcinoma of the stomach, carcinoma of the esophagus, gastric neurosis, pernicious anemia, secondary anemia, avitaminosis, cardiac decompensation, chronic nephritis with uremia, diabetes mellitus, gall stones, hypertension, hyperthyroidism, syphilis and normal individuals. Commercial trypsin and pancreatin were used. Bile was obtained from patients during operation. Ordinarily Lilly's U-20 insulin was employed. The rabbits used in the tests weighed about 5 pounds.

Plan of Investigation. The method consisted in mixing from 1 to 10 cc. (usually 10 cc.) of gastric juice with 20 units of insulin and incubating for 1 hour at 37° C. In some experiments the mixtures were incubated for as short a period as 5 minutes. The amount of free and total acid in the gastric juice was determined in each specimen. The free acid varied from 0 to 80, and since the amount of acid appeared to have no relation to the results, the individual figures for the acid will not be given. When pancreatin and trypsin were tested about 5 gm. of each was mixed with water, and the same procedure followed as with gastric juice.

The mixtures were injected intramuscularly into rabbits, and blood samples were obtained from the ear veins before the injection and afterward in $\frac{1}{2}$, 1, 2, 3 or more hours. The blood sugar* was determined according to the micro method of Folin.[18]

The method of insulin extraction was as follows: Eight parts of 95% alcohol were added to 1 part of the insulin-gastric juice mixture, thoroughly mixed and centrifuged. Since 10 cc. of gastric juice were mixed usually with 1 cc. of U-20 insulin, it required 88 cc. of 95% alcohol for the extraction of insulin. The supernatant fluid was removed and evaporated down to 1 or 2 cc. or to dryness *in vacuo* at a temperature of not more than 37° C. This was made up with distilled water to a volume of 10 cc. and injected into rabbits.

* Miss Honora F. Carroll gave technical assistance.

Effect of Gastric Juice on Insulin. The effect of gastric juice on insulin was studied first. A typical example of the results of the blood sugar determinations obtained in the rabbits after the injection of the insulin-gastric juice mixture is given in Chart 1. The results were all much alike. After the injection there was no drop in the blood sugar level such as is seen when 20 units of insulin alone are injected. Instead, there was usually a rise in the blood sugar of 5 to 25 mg. usually in ½ or 1 hour after the injection and then a drop to near the original blood sugar level during the 3 or 4-hour period of observation.

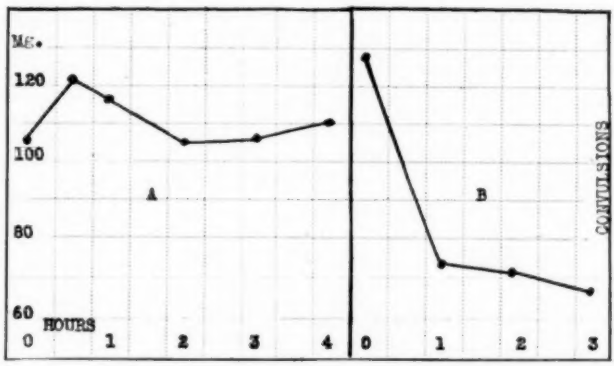

CHART 1.—Comparison of blood sugar curves obtained in a rabbit *A*, after the injection of 20 units of insulin incubated with gastric juice, and *B*, after the injection of 20 units of insulin in one leg and gastric juice in the other.

From these experiments it appeared that insulin was digested or inactivated by the gastric juice, even in the experiments where the insulin and gastric juice were incubated for as short a period as 5 minutes. In order to determine whether the insulin was simply inactivated, an effort was made to extract insulin from the incubated insulin-gastric juice mixture according to the method described.

The extract was injected and the blood sugar curves were observed for a period of 3 or 4 hours. The results obtained were much the same as those obtained following the injection of the incubated insulin-gastric juice mixture. This suggested that the insulin was digested, completely destroyed and could not be recovered.

Prevention of Insulin Digestion by Gastric Juice. The next step in this investigation consisted in trying to prevent insulin from being digested by gastric juice. At first an attempt was made to confirm the reported protective ability of blood serum, saline, Ringer's solution and saponin on insulin. Varying amounts of these substances were added to 20 units of insulin and incubated at 37° C. for 15 to 30 minutes. Then 10 cc. of gastric juice were added to each specimen, incubated for 1 hour and injected into rabbits. The

blood sugar curves showed no drop in the blood sugar level during the periods of observation. The results indicated quite clearly that blood serum, saline, Ringer's solution and saponin did not prevent gastric juice from destroying insulin.

It then seemed logical to try to protect insulin from digestion by dissolving or combining it with some chemical which is readily absorbed from the gastro-intestinal tract. Since insulin in alcoholic solution administered by mouth has been reported to cause a reduction in the blood sugar, alcohol was selected for this purpose. These experiments were conducted by dividing specimens of gastric juice into two equal parts of usually 10 cc. To one part, 20 units of insulin were added and incubated for 1 hour. This was injected into a rabbit, and the blood sugar curve was observed for 3 hours to serve as a control test. Then 20 units of insulin were dissolved in 10 cc. of 95% alcohol and incubated for 5 to 10 minutes. To this the second part of gastric juice was added and incubated for 1 hour. Since alcohol is irritating when injected, the insulin was extracted in the usual manner. This extract was injected, and the resultant blood sugar curves were determined.

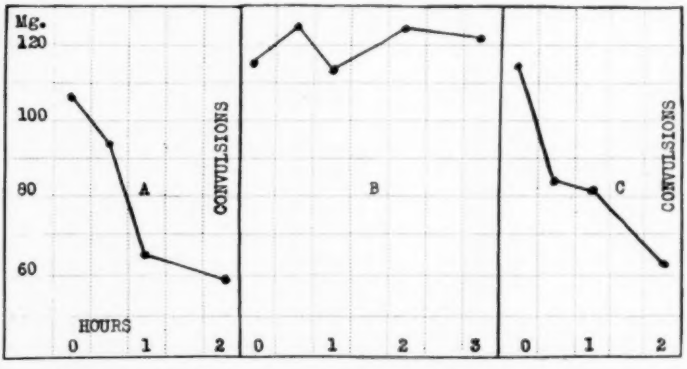

CHART 2.—Characteristic blood sugar curves obtained in a rabbit *A*, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with gastric juice, *B*, after the injection of 20 units of insulin incubated with gastric juice, and *C*, after the injection of 20 units of insulin.

The results obtained were very striking and interesting. In the control tests the blood sugar concentration varied very little after the injection of the insulin-gastric juice mixture. However, the blood sugar curves following the injection of the extract from the mixture in which the insulin was protected with alcohol were quite different. A typical illustration of the results obtained is given in Chart 2. There was a marked reduction in the blood sugar level and the rabbits had convulsions usually in 2 hours and occasionally in 1 or 3 hours after the injection. The resultant blood sugar curves

were similar to those obtained when 20 units of insulin were injected. These results suggested that alcohol protected insulin from digestion by gastric juice, or that alcohol destroyed the enzymes in the gastric juice, thus preventing the digestion of insulin.

The experiments were repeated in an endeavor to protect insulin with varying quantities and concentrations of alcohol. The results obtained with as little as 5 cc. of 95% alcohol or 10 cc. of 48% alcohol were much the same as when 10 cc. of 95% alcohol were employed. However, when smaller amounts or concentrations of alcohol were used there was usually only a slight drop in the blood sugar level.

It was then ascertained whether alcohol destroyed the enzymes in the gastric juice. This was accomplished by mixing 10 cc. of 95% alcohol with 10 cc. of gastric juice and incubating for 1 hour. The alcohol was evaporated off *in vacuo*, and 20 units of insulin were added. This was incubated for 1 hour and injected.

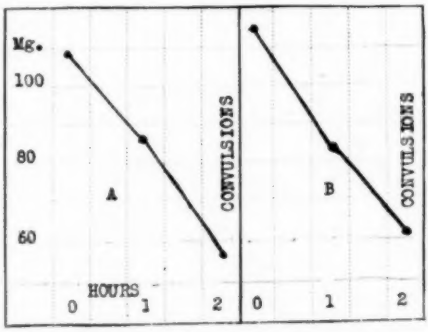

CHART 3.—Relative blood sugar curves obtained in a rabbit *A*, following the injection of 20 units of insulin incubated with gastric juice to which alcohol was added and evaporated off, and *B*, after the injection of 20 units of insulin.

The findings were all much the same as those noted when the alcohol was added first to the insulin. An illustration of the blood sugar curves obtained in the rabbits after the injection of this mixture is shown in Chart 3. These results suggested that alcohol destroyed the enzymes in the gastric juice and thus prevented the destruction of insulin.

It seemed important to learn whether alcohol entered into any chemical combination with insulin and thus prevented it from being digested. To study this aspect of the problem the experiments were repeated by adding 10 cc. of 95% alcohol to 20 units of insulin. This was incubated for 1 hour and evaporated to dryness *in vacuo*. Then 10 cc. of gastric juice were added and incubated for 1 hour. This was injected, and the blood sugar level was observed over a period of 3 to 5 hours.

The blood sugar curves obtained in these tests were not remark-

able. There was only a slight maximum reduction of 10 to 33 mg. in the blood sugar concentration in 2 or 3 hours after the injection, and in some experiments there was no decrease in the blood sugar. A typical example of the results is shown in Chart 4. Apparently insulin and alcohol did not enter into any combination to protect it from digestion after the evaporation of the alcohol.

The results in general suggested that alcohol protects insulin chiefly by inactivating the peptic enzymes and thereby preventing the gastric juice from destroying insulin.

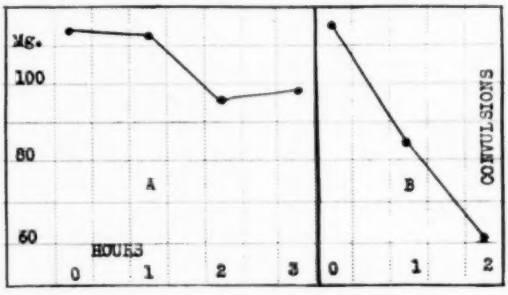

CHART 4.—Blood sugar curves obtained in a rabbit *A*, after the injection of gastric juice incubated with 20 units of insulin which was dissolved in alcohol and evaporated to almost dryness, and *B*, after the injection of 20 units of insulin.

Effect of Trypsin, Pancreatin and Bile on Insulin. The effect of intestinal enzymes on insulin, with and without alcohol, was investigated. A small amount of powdered trypsin was mixed with 20 cc. water and divided into two parts. To one part 20 units of insulin were added and incubated for about 40 minutes, and then injected. To the second part 20 units of insulin dissolved in 10 cc. of 95% alcohol were added and incubated for about 40 minutes. The insulin was extracted and injected, and the blood sugar levels were determined over a period of 3 hours. After the injection of the first part into rabbits there was very slight variation in the blood sugar level. In contrast, after the injection of the second part, there was a sharp drop in the blood sugar level. Typical illustrations of the results are shown in Chart 5. These results suggested that trypsin, like gastric juice, destroyed insulin, and this digestion was prevented when the insulin was dissolved in alcohol.

The same type of experiments were made using pancreatin instead of trypsin. Similar findings were noted and typical examples are shown in Chart 6.

The effect of bile on insulin was tested by adding 20 units of insulin to 10 cc. of bile and incubating for 1 hour. This was injected and the resultant blood sugar curves were compared with those observed when bile alone was employed. The bile was obtained at operation on patients who had gall bladder disease. In 2 cases the

bile was taken from the gall bladder and in 1 case from the gall-bladder and common duct simultaneously. The results obtained were variable as shown in Chart 7. For example, in 1 case, after the injection of the insulin-bile mixture, there was a maximum de-

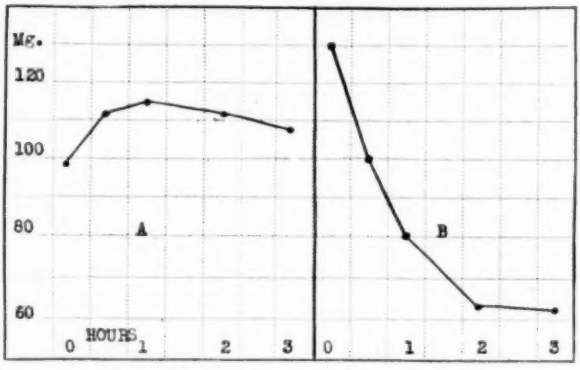

CHART 5.—Comparative blood sugar curves obtained in a rabbit *A*, after the injection of 20 units of insulin incubated with trypsin, and *B*, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with trypsin.

crease of only 40 mg. in the blood sugar level, whereas in another case, there was a marked drop in the blood sugar level and the rabbit became convulsed within 3 hours. When bile was injected there was no significant change in the blood sugar concentration. These results suggested that bile is probably not a very significant factor

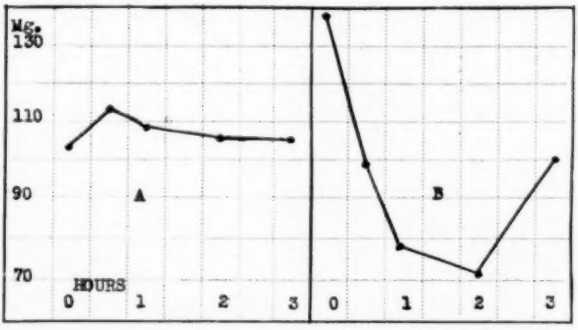

CHART 6.—Blood sugar curves obtained in a rabbit *A*, after the injection of 20 units of insulin incubated with pancreatin, and *B*, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with pancreatin.

in the inactivation of insulin. Nevertheless, it may be to some extent an inhibitory factor in certain cases with gall bladder disease.

The Oral Administration of Insulin in Alcohol. As the result of the previous experiments, it was reasonable to conclude that insulin

dissolved in a sufficient amount of alcohol with a proper concentration was not destroyed by gastric juice, trypsin or pancreatin. An attempt was made to determine whether or not this fact can be made of clinical value in the treatment of diabetes mellitus. Seven diabetic patients and three rabbits were given orally 40 to 200 units of insulin in 30 to 60 cc. of 48% alcohol to study this phase of the problem.

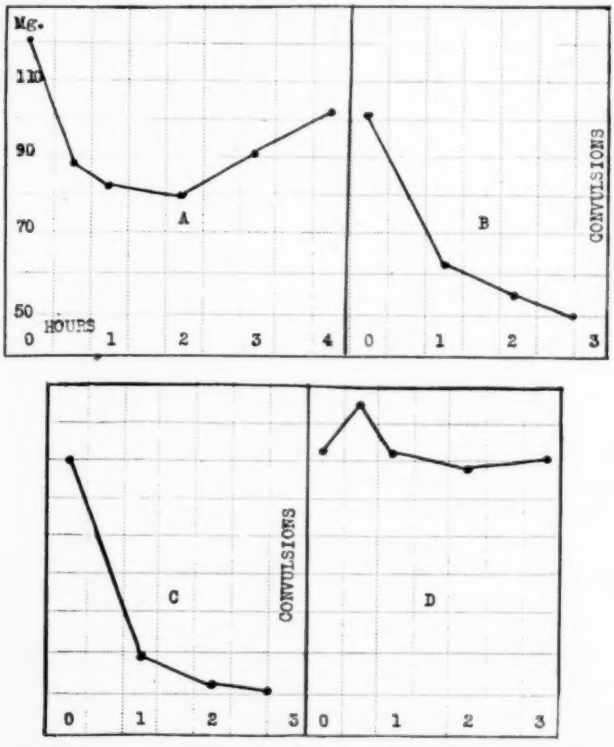

CHART 7.—Relative blood sugar curves obtained in a rabbit after the injections of *A*, 20 units of insulin incubated with bile from the gall bladder of a patient, *B* and *C*, 20 units of insulin incubated with bile obtained from the gall bladder and common duct respectively of another patient, and *D*, bile.

The blood sugar concentration was determined fasting and at hourly intervals for 6 hours after the intake of the alcoholized insulin. These blood sugar curves were compared with those obtained when alcohol alone was ingested. The results were disappointing. In the patients with diabetes after the ingestion of the alcoholized insulin there were maximum reductions of 46 to 129 mg. during the periods of observation. Nevertheless, these results were not significant because the maximum decreases observed in the

corresponding control tests were practically identical. In the rabbits there was also no important variation in blood sugar level following the intake of the alcoholized insulin. In 1 patient with diabetes 100 units of insulin in 30 cc. of 95% alcohol was introduced into the duodenum with a stomach tube and under the fluoroscope. The resultant blood sugar curve was insignificant.

The cause of these failures was investigated by administering orally 100 units of insulin dissolved in 30 cc. of 95% alcohol to 7 patients. The gastric contents were aspirated in ½ to 1 hour, and an attempt was made to extract insulin. The extracts were injected into rabbits, and the resultant blood sugar curves were determined. From the results obtained it appeared that a large amount of insulin was recovered in 1 case, small amounts in 3 cases and no insulin in 3 cases. In the last 3 cases it was difficult to tell whether the insulin had been digested in the stomach or whether the insulin had passed out of the stomach into the intestine and could not be aspirated. However, in 4 cases at least it could be demonstrated that the insulin in alcohol was not digested entirely in the stomach in ½ or 1 hour's time.

It appears from this work that insulin in alcohol, administered orally, has no significant effect on the blood sugar due to the lack of absorption from the gastro-intestinal tract. On the other hand, it is possible that the alcohol becomes absorbed and allows the insulin to be destroyed by the enzymes.

Summary. This paper presents a study on the effect of gastric juice, trypsin, pancreatin and bile on insulin and the protection of insulin with alcohol from digestion in 116 experiments.

The results suggest that these enzymes, except bile, digest and render insulin inactive *in vitro*. This effect does not occur when insulin is dissolved in alcohol. The protection thus afforded is probably caused by the destruction of the digestive enzymes by alcohol and not that insulin enters into any special combination with alcohol.

Insulin in alcohol administered by mouth has no significant effect on the blood sugar level. This is probably due to the lack of absorption of insulin from the gastro-intestinal tract although it is possible that the alcohol becomes absorbed and allows the insulin to be destroyed by the enzymes *in vivo*.

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THE ADVANTAGES OF VACUUM DRIED COMPLEMENT FOR USE IN THE ROUTINE WASSERMANN REACTION.

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and
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Flosdorf and Mudd[1] have recently described a vacuum apparatus for dehydrating serum from the frozen state. The term "lyophile" has been applied to the dehydrated product. Eagle, Strauss and Steiner[2] have pointed out the advantage of lyophile complement as compared with other methods of preserving complement. They ran Wassermann tests with 3477 sera and spinal fluids and obtained results using lyophile complement which were indistinguishable from complement freshly bled and salted for use within a 3 to 4-day period.

Through the coöperation of Dr. Harry Eagle we have obtained sufficient lyophile complement to permit us to use it exclusively in our routine Wassermann tests. It has been supplied in lots of from 100 to 300 cc., distributed in small vials containing from 8 to 12 cc. each. They were kept at 8 to 10° C., and were sealed before removal from the lyophile apparatus so that the dry complement was kept in vacuum. When needed for use, distilled water was added in amounts

equal to the original amount of complement. As nothing but water was removed from the complement during the dehydration process, only water was replaced. Upon the addition of the water, the dry porous material rapidly dissolved and the solution resembled fresh complement as far as could be determined. A vial from each lot was tested for hemolytic activity before it was accepted for routine use.

We have used this lyophile complement in our routine Wassermann tests for over a year and a half. During this period Wassermann tests were conducted 3 times a week. Tests were performed upon 12,175 sera and 675 spinal fluids. Fourteen lots of complement have been used and over 250 vials have been titrated and used in these tests. Not once has the lyophile complement proven unsatisfactory, or the cause of any irregularity in the tests. The advantage of having satisfactory complement ready for use at any time is obvious. The uniformity in the potency of lyophile complement can be attributed to the fact that the sera of a larger number of guinea pigs can be pooled than is ordinarily the case.

Stability of Lyophile Complement. Eagle, Strauss and Steiner have shown that lyophile complement retains its hemolytic activity for at least 8 months. This was the longest period tested. For the purpose of studying the stability, we set aside a vial or two from each lot of lyophile complement when received. These vials were tested at intervals to represent complement of various ages. One hemolysin was used in this series of tests which was designated as Hemolysin B. It was about 2 years old when the tests were started and its titer was fairly stationary. At intervals its titer was determined with fresh complement. Table 1 shows the hemolytic activity of lyophile complement of various ages, and also the result of the complement titration which was done at the same time using two units of hemolysin.

A study of Table 1 shows that all lots of lyophile complement ranging in age from 1 to 52 weeks inclusive had satisfactory hemolytic activity when compared with fresh complement. It appears from these tests that there was no loss of activity up to and including 52 weeks. The five lots which were over 52 weeks of age (55, 56, 58, 59 and 60 weeks), all showed some loss of hemolytic activity. Three of the five showed sufficient activity to give satisfactory complement titrations with two units of hemolysin. Confirming these results, obtained in actual practice, Eagle (personal communication) has found that the dehydrated complement generally begins to show demonstrable deterioration after 12 months storage in the refrigerator. It is quite possible that with technical improvements in the lyophile process, longer periods of perservation may be achieved.

Fixability of Lyophile Complement. It was thought advisable to determine whether lyophile complement of at least a year old was as readily fixed as fresh complement in the Wassermann reaction. For this purpose several positive sera were tested at the same time

TABLE 1.—HEMOLYTIC ACTIVITY OF LYOPHILE COMPLEMENT.

	Age of Complement (weeks).	1	2	2	3	5	5	6	6	9	10	11	14	16	20	36	36	37	47	49	0	0	52	0	52	52	55	0	56	58	59	60	0
Hemolysin titration (hemolysin B)	1 to 32,000																																
	1 to 24,000		x		x																												
	1 to 20,000								x											x			x					x					
	1 to 16,000	x		x				x			x	x	x					x			x	x		x	x								x
	1 to 12,000					x	x			x				x	x	x	x		x							x							
	1 to 10,000																																
	1 to 8,000																												x				
	1 to 6,000																										x				x		
	1 to 5,000																													x[a]		x[b]	
Complement titration	0.5 cc.																																
	0.45																																
	0.40																																
	0.35													x	x											x			x		x		
	0.30			x		x	x	x	x	x						x	x		x				x				x						
	0.25	x	x		x						x	x	x					x		x	x			x									x
	0.20																											x					
	Lot No. of Complement	2	3	3	1	5	7	6	1	8	12	9	10	11	14	4	5	9	4	3	F	F	6	F	10	14	11	F	13	8	9	11	F

a = Incomplete hemolysis in 1 to 5,000 dilution with cells 4, 7 and 11 days old.
b = Incomplete hemolysis in 1 to 1,000 dilution.
F = Fresh complement.

with lyophile complement 56 weeks old and fresh complement. The complement used was lot 13 which, as shown in Table 1 had lost some of its hemolytic activity but still gave a satisfactory complement unit when tested with two units of amboceptor. The results obtained indicate that the lyophile complement was just as readily fixed as fresh complement.

TABLE 2.—A COMPARISON OF THE FIXABILITY OF FRESH AND 56 WEEKS OLD LYOPHILE COMPLEMENT.

Amount of serum.	Serum No. 1.		Serum No. 2.		Serum No. 3.		Serum No. 4.		Serum No. 5.	
	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.
0 2 cc.	4	4	4	4	3	3	±	±	4	4
0 1 cc.	4	4	4	4	1	±	—	—	4	4
0 05 cc.	3	3	2	2	—	—	—	—	3	2
Control	—	—	—	—	—	—	—	—	—	—

Additional evidence of the fixability of lyophile complement is shown in the results of a study of 646 sera from known syphilitics in which the Wassermann test using lyophile complement was compared with the Kahn and Eagle flocculation tests. The Wassermann test in this series proved to be as sensitive as the Kahn test. A complete report of these tests will be published elsewhere.[3]

Conclusions. Complement dehydrated from the frozen state and sealed *in vacuo* ("lyophile" complement), when stored in the refrigerator at 8° to 10°C. retained its full hemolytic activity and fixability for a period of 12 months. Both the complement and hemolysin titrations remained approximately constant over this entire period. Thereafter deterioration was detected. This complement has been used in 12,175 blood and 675 spinal fluid Wassermann tests and has proved in all respects equivalent to fresh complement. We have discontinued our guinea pig colony because of the greater convenience and uniformity of this type of complement.

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BOOK REVIEWS AND NOTICES.

TWENTIETH CENTURY PSYCHIATRY. Its Contribution to Man's Knowledge of Himself. By WILLIAM A. WHITE, M.D., M.A., Sc.D. Pp. 198. New York: W. W. Norton & Co., Inc., 1936. Price, $2.00.

THIS volume is one of the series based on the Salmon Memorial Lectures. It is concerned with psychiatry as a medical specialty, the social significance of psychiatry and the general implications of psychiatric thought. Of this period was Kraepelin, whose outstanding achievements were in the dementia præcox and manic depressive psychoses. At about the same time Binet and Simon did their research in feeble-mindedness and developed their intelligence scale. Freud, elaborating upon the studies of Janet, gave us psychoanalytic psychology. America's contribution was mental hygiene, with which movement Salmon was so intimately identified, and which now lays claim to branches in all civilized countries.

In the discussion the increasing number of psychiatric patients, the movement to keep them at home as long as possible is heartily approved. For many centuries this method has been in operation in Gheel, Belgium, but the author does not mention its recent employment in Massachusetts and New York.

This thesis shows a compromise between a technical and a popular rendering, giving consideration to aphasia, crime trials with their absurd hypothetical questions, "gestalt" psychology, heredity, sterilization and diverse other subjects. N. Y.

DENTAL INFECTION AND SYSTEMIC DISEASE. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division, Cleveland Clinic, etc. With a Foreword by DR. EDWARD C. ROSENOW, Pp. 163; 63 illustrations. Second edition, revised. Philadelphia: Lea & Febiger, 1936. Price, $2.50.

AN accurate and convincing presentation of an important subject. There are discussed the bacteriology of dental infection, with a most interesting correlation of culture findings with radiographic and clinical examinations of pulpless teeth; the pathogenicity of the organisms found in dental infection; the types of diseases which may arise from dental focal infection; the experimental proof for the relation of infected teeth to such metastatic disease. The book is warmly recommended both to physicians and dentists. R. K.

AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS. By various writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D., (OXON.), F.R.C.P., (LOND.), Consulting Physician to Guy's Hospital; late Physician to H. M. Household. Pp. 1145; 742 illustrations (196 in colors). Fifth edition. Baltimore: William Wood & Co., 1936. Price, $16.00.

NEW diagnostic tests are devised from time to time; many of these do not survive, but a few prove themselves to be of permanent worth—the Aschheim-Zondek test for pregnancy, for example; the technique of established methods improves—pyelography, for instance, and methods of exam-

ining the gall bladder and the Fallopian tubes have made great strides in the last few years; rare diseases such as tularemia, botulism, psittacosis, pink disease, become less unfamiliar; the result being that, although the main factors in differential diagnosis are permanent, this work has to be re-edited from time to time.

Many tests have been omitted purposely, on the ground that, as laboratory methods, their bed-rock reliability has not yet been established; but it is hoped that all those on which reliance can be placed have been included.

The original purpose of the work remains unchanged; it is intended to be a help in arriving at a correct diagnosis in cases in which one or more symptoms are pronounced and yet the real nature of the malady is not immediately clear. It would seem that the book serves a useful purpose for it has already reached its 53rd thousand. (From the Preface to the fifth edition.)

AMERICAN MARTYRS TO SCIENCE THROUGH THE ROENTGEN RAYS. With a Short Glossary of the Scientific Terms Used in the Text. By PERCY BROWN, M.D., F.A.C.P., F.A.C.R., Historian and Former President, American Roentgen Ray Society. Pp. 276; 55 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $3.50.

THIS record of the lives of 28 American martyrs to the infant science of Roentgenology is indeed a labor of love by one who was the "dear friend" of most of them and himself has not come unscathed through his service to the cause. "Martyrs" also in the etymological sense of witnesses to the truths of the discipline to which their lives were sacrificed, these men (and one woman) without exception continued in the path of duty, unflinchingly and heroically, even when in most cases some of the perils of continued activity were appreciated and all possible efforts to meet these perils were made. It is good to have on record an accurate contemporary account of such men's lives, of which already some of the details were fading from view; it is still better to know that the list of sacrifices to this particular risk from now on will not be greatly increased; but perhaps best of all is to have before us the stimulating example of these unassuming heroes in their careers of unswerving devotion. E. K.

INSULIN. ITS PRODUCTION, PURIFICATION AND PHYSIOLOGICAL ACTION. By DOUGLAS W. HILL, B.SC. (BRIS.), PH.D. (LIV.), Lecturer in Chemistry, University College, Exeter; Special Lecturer in Organic Chemistry, University of Bristol, and FREDERICK O. HOWITT, M.SC., PH.D. (LOND.), F.I.C. Foreword by Professor E. C. DODDS. Pp. 219; 6 photomicrographs and 7 tables. London: Hutchinson & Co., Ltd., 1935. Price, 12/6.

THIS monograph, for its size, covers the vast amount of literature on insulin in a surprisingly complete manner. In addition to author and subject index there are 9 chapters which not only deal with insulin but treat briefly the subjects of carbohydrate metabolism, methods for the quantitative determination of glucose, and insulin substitutes. A bibliography at the end of each chapter includes a total of over 1500 references. As the literature is so great, the authors have omitted any discussion of the clinical use of insulin. The relation of the pancreas to the other glands of internal secretion has been discussed but briefly. Anyone interested in the scientific development, and physiologic action of insulin will find this book most interesting and instructive. J. J.

CANCER COMMISSION COMMITTEE STUDIES. The California Medical Association. (The Results of a Five-year Correlated Study by 150 Members of the Medical Profession.) Pp. 123. San Francisco: J. W. Stacey, Inc., 1936. Price, 75c.

THIS booklet reproduces material published in *California and Western Medicine* by the Cancer Commission created by the California State Medical Society in 1931. It includes concise statements from 13 committees mostly dealing with tumors of various parts of the body. While the several reports necessarily vary considerably in form and merit, they can be said to give, in general, clear statements of the kinds of tumors met and their manifestations, with sound advice as to treatment. To a pathologist, the pathologic aspects seem scantily treated even in such a practical compilation; for instance, no statements were found about such an important matter as the biopsy and the evaluation of malignancy. Representing the views of over 150 practitioners, however, this work epitomizes in convenient form a valuable cross sectional modern view of cancer. E. K.

A GUIDE TO PSYCHIATRIC NURSING. By F. A. CARMICHAEL, M.D., Superintendent, Osawatomie Hospital, Osawatomie, Kansas; Lecturer in Clinical Psychiatry, University of Kansas Medical School, Kansas City, and JOHN CHAPMAN, M.A., M.D., Sometime Associate in Psychiatry, Osawatomie State Hospital, Osawatomie, Kansas. Pp. 175; 31 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $2.25.

THIS is a small book organized for a course in psychiatric nursing and is somewhat comprehensive although concise. Having been written primarily for a State Hospital it is essentially clinical and practical.

One chapter deals entirely with the symptomatology of mental disease and its relation to care and treatment from the nursing standpoint. A good résumé on the history of psychiatry is given; a chapter on psychopathology is quite comprehensive and fairly liberal in its presentation.

Chapters on etiology and a description of the psychoses follow a clinical pattern. Although the practical application of nursing principles and technique are stressed the writers are physicians rather than nurses and the emphasis lies on theory as well as practice.

As a textbook for nurses in general training it might be too profound. For nurses taking postgraduate psychiatric work it would probably be more suitable.

In the appendix one of the authors submits a modification regarding the classification of mental disease on the basis of the description of the activity of the patient rather than the emotional state. This is out of place in the book and although interesting would not be agreeably received in many psychiatry circles. L. S.

BASAL METABOLISM IN HEALTH AND DISEASE. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College, New York; Physician in Chief to the New York Hospital. Pp. 494; 99 illustrations and 67 tables. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $5.00.

"THE subject of basal metabolism has during the last few years become of considerable importance to the practitioner of medicine. Most of the literature which deals with it, however, is written primarily for research workers or physiologists. The writer has, therefore, attempted to bring

basal metabolism out of the realm of pure physiology into the domain of clinical medicine. This book is written for those engaged in the practice of medicine and surgery, for medical students, for physiologists and for dietitians. While it has not seemed necessary to give the details of the many instruments used for measuring the basal metabolism, the underlying principles of technique have been fully discussed.

"The chapters dealing with surface area and normal standards have been rewritten and rearranged in the light of the contributions of the last two years and the chapters on disease have received many additional references.

"The advance in the study of basal metabolism is not unlike the settlement of a new colony in a distant land. When the first edition of this book was written in 1924 most of the pioneers, Rubner, Zuntz, von Müller, Magnus-Levy, Benedict and Lusk were still active in the field. The frontier was expanding. At the time of the second edition in 1927 there had been a great stabilization but there was still much unexplored territory and not a few outposts in dangerous or sterile regions that have since been abandoned. The third edition comes in a period of well established settlements and relatively little exploration into new country. One important field dealing with physical channels of heat loss is, however, yielding much information and it has been a pleasure to add a new chapter on this subject." (From Author's Preface.)

GENETICS. By H. S. JENNINGS, Henry Walters Professor of Zoölogy and Director of the Zoölogical Laboratory in the Johns Hopkins University. Pp. 373; 70 illustrations. New York: W. W. Norton & Co., Inc., 1935. Price, $4.00.

THE resemblances and differences among organisms depend upon two main factors. First, upon the material received from their parents, and second, upon conditions to which this material has been subjected. It is with the first of these factors, heredity (or, more broadly, genetics) that this books deals. The author has aimed to present his subject in such a manner that any educated person may understand it. Hence this work may be read with profit not only by the physician but by the ever increasing group of laymen whose intellectual curiosity has been stimulated by the great discoveries made in the field of genetics. Among the subjects discussed are the materials of heredity and their operation, the germ cells and the chromosomes, the genes and their relation to characteristics, the rules and ratios of inheritance, the relation of characteristics to environment, the interaction of environment with heredity, hybridization, genetic variations and mutations.

Professor Jennings' lucid presentation of his subject makes the book very readable. B. L.

POSTMORTEMS AND MORBID ANATOMY. By THEODORE SHENNAN, M.D., F.R.C.S. (EDIN.), Professor of Pathology in the University of Aberdeen. Pp. 716; 241 illustrations. Third edition. Baltimore: William Wood & Co., 1935. Price, $9.00.

THIS book deals with the technique of postmortem examinations and with the study of the organs as they are seen at the autopsy table. Of particular value are the instructions of how to examine each organ. First, in the case of the lung, it is stated that the principal points to be investigated are: the color of the organ, the air-content, consistency, friability, presence or absence of consolidation, the nature of the fluid escaping from the cut surfaces and from the bronchi, and the nature of abnormal cavities. Under

these several headings there is a very useful discussion which should serve as a guide not only to the undergraduate but prove of considerable help to the practising physician who occasionally has an opportunity to perform an autopsy. The book is well written and has excellent illustrations. That a third edition was demanded speaks for its continued usefulness.

B. L.

INJURY AND INCAPACITY. With Special Reference to Industrial Insurance. By H. ERNEST GRIFFITHS, M.S. (LOND.), F.R.C.S., Surgeon, Albert Dock and Hertford County Hospitals; Consulting Surgeon, Wimbledon Hospital, etc. Pp. 270. Baltimore: William Wood & Co., 1935. Price, $5.00.

THE object of this book is to place in the hands of interested individuals a compilation of the experience gained in the handling of industrial cases. Its basis has been the records of some 50,000 case reports of a large English insurance company and some 15,000 of his own cases. He attempts to form an estimate of the probable period of disability based upon the statistical analysis of these cases. The subject matter has been arranged in anatomical groupings, *e. g.*, disabilities following injuries to the head, chest, and so on. In each group he discusses the cause of the disability, the symptoms which may arise as sequela of the injury and at the end of each section there is appended a table setting forth the statistical experience of the "average period of the incapacity from work." The estimates are given for both heavy and light work and they are further subdivided according to age and in some cases according to sex. In many of the sections, suggestions as to treatment are given from the experience of the author.

At the end of the book, the author has appended a classification of the physical requirements for particular trades. He has classified all occupations into 24 types and he describes in detail the necessary physical requirements for workmen employed in a particular trade. Thus, in Type I, the physical requirements are given for heavy, laborious work and all forms of labor on the flat; Type IV gives the requirements for electricians; Type XI, for dressmakers; Type XXIII, for crossing-sweepers, and so on. In this analysis the author points out the necessary functions and shows how certain anatomic disabilities such as loss of a finger or, in some cases, ankylosis of joints may not necessarily be disabling for certain occupations.

The book has no illustrations; it is clearly and concisely written and should have a large field of usefulness for both medical men and lawyers who are interested in industrial surgery.

L. F.

THE HAIR AND SCALP. A Clinical Study (with a Chapter on Hirsuties). By AGNES SAVILLE, M.A., M.D. (GLASG.), M.R.C.P.I., Consulting Physician to Fitzroy Square Skin Hospital, etc. Pp. 288; 54 illustrations. Baltimore: William Wood & Co., 1935. Price, $5.00.

THOSE who have mourned the gradual passing of Jackson and McMurtry's book on diseases of the scalp from our dermatologic shelves will welcome Saville's effort to bring our somewhat tattered and discreditable knowledge of hair and scalp diseases up to date. The book contains a great deal of information, as systematically arranged on the whole as a subject of such patchwork knowledge could be. It is really remarkable to find how often the search for information on an individual point is rewarded by an excellent paragraph or two containing a discriminating review of the most recent investigations. The book follows the clinical tradition of English dermatology, but gives more than the usual regard for general

opinion and the results of special investigation by students in many fields and in the best known Continental and other groups. The approach on controversial matters is temperate and broad, as witness the account of the legendary sudden whitening of the hair. There are a number of excellent case illustrations from the author's evidently very substantial experience in the treatment of disease of the hair and scalp. The chapter on hirsuties will add a point or two to almost anyone's armamentarium of information and therapeutic crutches in such situations. The constitutiona background of hair and scalp disease receives remarkable and discriminating attention, while the local management, even to the effect of modern cosmetic practices and foibles is well dealt with. The chapter on the molecular structure and elastic properties of hair, written by W. P. Aspbury, Lecturer on Textile Physics in the University of Leeds, is a genuine piece of first-rate research which has direct application, as Saville points out, to such common practices as the "permanent wave." The classifications are in the main clinical and morphologic rather than etiologic, but of course, unavoidably so. It has been necessary to lump large blocks of clinical phenomena into single patchwork chapters, such as that on pustular conditions of the scalp. This method of treatment, while regrettable as an evidence of incomplete knowledge, is a convenience from the standpoint of the clinician and practitioner. The observations on hair dyes are discriminating, useful and complete. It would seem that authors contemplating publication in a foreign country could afford to make their therapeutic recommendations and prescriptions conform more closely to the pharmacopeial terminology of their publisher's market, and this book cannot wholly escape this criticism. The useful memoranda on formulæ are, however, almost uniformly usable in American practice. For a book which happily escapes the current exploitation by and misuse of colored plates, the price seems unduly high, and will perhaps limit its usefulness regrettably to the practice of specialists.

J. S.

THE RADIOLOGY OF BONES AND JOINTS. By JAMES F. BRAILSFORD, M.D. (B'HAM.), M.R.C.S. (ENG.), Hunterian Professor, Royal College of Surgeons, England, 1934–1935; Radiologic Demonstrator in Living Anatomy, The University of Birmingham, etc. Pp. 571; 340 illustrations. Second Edition. Baltimore: William Wood & Co., 1935. Price, $9.00.

THOUGH appearing but one year after the first edition, several notable changes have been made in this excellent textbook. A chapter on Dental Radiography has been added. Several sections have been rewritten as the result of recent investigations. Some of the illustrations have been replaced.

G. W.

GREAT DOCTORS OF THE NINETEENTH CENTURY. By SIR WILLIAM HALE-WHITE, K.B.E., M.D., LL.D. (HON.), F.R.C.P., Consulting Physician to Guy's Hospital. Pp. 325. Baltimore: William Wood & Co., 1935. Price, $5.00.

THE nineteenth was an eventful century through the contributions made to medical progress by outstanding individual British physicians and surgeons. The author has gathered together biographical sketches of 17 distinguished men whose particular contributions became of interest not only to medical men but to the general public as well. The series extends from the last years of the eighteenth century, when Jenner discovered vaccination, to the end of the first quarter of the twentieth century, when Ross confirmed his observations on the transmission of malaria by mosquitoes.

The series might be likened to a chain as the individuals became more or less intimately associated one with another, Astley Cooper, in the field of anatomy and surgery; Charles Bell, in comparative anatomy and musculo-nervous sensation; Bright in his exposition of the morbid anatomy of the kidney; Bowman, both by his discoveries in the histology and physiology of the kidney, and as ophthalmologist and physiologic histologist; Marshall Hall, with his method of reviving the asphyxiated and his investigations of the diseases of the nervous system; Addison, who achieved the distinction of discovering two diseases both named after him; Stokes, by attention to clinical investigation and clinical teaching, especially of the affections of the heart; Simpson, surgeon and anesthetist; Paget as surgical pathologist; John Simon, in Public Health; Gull, Wilkes and Hughlings Jackson in neurology; Lister, a surgeon practising antisepsis; Manson, detecting the effects of parasites in Tropical diseases; and, lastly, Ross discovering that the anopheles mosquito is the carrier of the malaria parasite.

Mingled with these names are those of hosts of others who by their labors either aided directly their chiefs, or helped to explain or elucidate what they had presented. Many were either directly connected with Guy's Hospital or were associated with Guy's men, so that it is of further interest to see the links which bound these men into such a continuous chain. The author is himself a "Guy's man," and the book can serve as an additional monument to the greatness of his predecessors in that Hospital.

The work is beatifully printed and the text most readable; its service could have been enhanced by the inclusion of contemporary portraits of their subjects. B. C.

MEDICAL MYCOLOGY. Fungous Diseases of Men and Other Mammals. By CARROLL WILLIAM DODGE, PH.D., Mycologist, Missouri Botanical Garden; Professor, Henry Shaw School of Botany, Washington University, St. Louis. Pp. 900; 142 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, $10.00.

IN this large volume, printed on good paper with a moderate number of line-drawings, the essentially medical, *i. e.*, disease, phases are sketchy, as might be expected where the author has the viewpoint of the cryptogamic botanist. However, in this field the greater need in medicine at present is the perspective and criticism of the botanist toward medical mycology, and these are amply and valuably expressed in this book. It is a very complete catalogue, analysis and critique of all of the fungous organisms known in mammalian disease, supplemented by a full bibliography. All of these are features which are not to be found in any other work on this subject in the English language. Keys are printed with the object of facilitating determination of species. It remains to be seen whether certain rather radical modifications of classifications, although they may be well founded botanically, will simplify an already difficult situation for the medical biologist. The book is an indispensable complement, biologically speaking, to the various treatises on clinical mycology which are widely and irregularly scattered through medical literature. F. W.

NEW BOOKS.

Collected Writings. Alfred F. Hess, 1875–1933. In 2 volumes. Pp. 1453; 127 illustrations, 124 charts and many tables. Springfield, Ill.: Charles C Thomas, 1936. Price, $15.00.

Neurological Surgery. By LOYAL DAVIS, M.S., M.D., PH.D., D.SC. (HON), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago. Pp. 429; 172 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1936. Price, $6.00.

Passive Vascular Exercises (and the Conservative Management of Obliterative Arterial Diseases of the Extremities). By LOUIS G. HERRMANN, A.B., M.D., Assistant Professor of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital, etc. With a Foreword by MONT R. REID, M.D. Pp. 288; 80 illustrations and 4 colored plates. Philadelphia: J. B. Lippincott Company, 1936. Price, $4.00.

The Baby and Growing Child. Feeding and Health Care for Physicians, Mothers and Nurses. By LOUIS FISCHER, M.D., Consulting Physician to the Willard Parker Hospital, New York City, and St. Vincent's Hospital, Montclair, N. J., etc. Pp. 260; many illustrations, some in colors. New York: Funk & Wagnalls Company, 1936. Price, $1.50.

Strength Out of Suffering. A Translation of Servitude et Grandeur de la Maladie. By FRANCE PASTORELLI. Pp. 224. Boston: Houghton Mifflin Company, 1936. Price, $1.50.

Chinese Medical Journal, Supplement No. 1, February, 1936. Pathology and Microbiology. Being Mainly Proceedings of the Chinese Society of Pathology and Microbiology held in Canton, November 5–8, 1935. Pp. 518; 70 plates of illustrations. Peiping: Chinese Medical Journal, 1936. Price, $2.50 or 10 shillings.

"Owing to the increasing number of papers in the field of Special Pathology and Microbiology hitherto published in the *Chinese Medical Journal* which is not primarily intended for such subjects, it is thought desirable to bring the material together in one publication; hence the issue of this first number of our Supplement series. This Supplement is of the same size and format as the regular issues of *Chinese Medical Journal* and contains over 500 pages of text and 70 plates of illustrations. Price, U. S., $2.50, or 10 shillings. The list of contents will give some idea of the value of this publication. It is hoped that all would-be contributors will read, learn and inwardly digest the article on 'Methods of Illustrating Scientific Papers,' the ignorance of which has spoilt many a promising reputation and the temper of many an editor." (Publisher's advertisement.) We heartily endorse the last paragraph.

Your Hay Fever. By OREN C. DURHAM, Chief Botanist, Abbott Laboratories, North Chicago, Ill. With an Introduction by MORRIS FISHBEIN and a Chapter on Treatment by SAMUEL M. FEINBERG, M.D., F.A.C.P. Pp. 264; 17 illustrations and 7 tables. New York: The Bobbs-Merrill Company, 1936. Price, $2.00.

On Percussion of the Chest. Being a Translation of Auenbrugger's Original Treatise Entitled "Inventum novum ex percussione thoracis humani, ut signo abstrusos interni pectoris morbos detegendi." [Vienna, 1761.] By JOHN FORBES, M.D. [London, 1824]. Introduction by HENRY E. SIGERIST. Pp. 31; 2 illustrations. Baltimore: The Johns Hopkins Press, 1936. Price, 75c.

The International Medical Annual. Fifth-Fourth Year, 1936. A Year Book of Treatment and Practitioner's Index. Editor: H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S.; B.Sc., F.R.C.S., with 36 Contributors. Pp. 555; 73 illustrations and 81 plates, some in colors. Baltimore: William Wood & Co., 1936. Price, $6.00.

Doctor of the North Country. By EARL VINTON MCCOMB, M.D. With a Preface by LOGAN CLENDENING, M.D. Pp. 238. New York: Thomas Y. Crowell Company, 1936. Price, $2.00.

A Textbook of Histology. By JOSEPH KRAFKA, JR., PH.D., M.D., Professor of Microscopic Anatomy, University of Georgia, School of Medicine, Augusta, Ga. Pp. 246; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, $2.50.

International Clinics. Vol. II, Forty-sixth Series, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 327; illustrated. Philadelphia: J. B. Lippincott Company, 1936.

The opening article of this number on Glomal Tumors (by Geschickter) includes an excellent colored illustration (Masson's trichrome stain) and a good exposition of the pathology of the subject. Of the 14 articles, 2 others are surgical, 2 pediatric and the rest medical.

Illustrous Contributions to Public Health. A Souvenir. Prepared for the Dedication Exercises on Tuesday, November 26, 1935. By CHARLES FREDERICK BOLDUAN, M.D., Department of Health, City of New York. Pp. 33; illustrated. Privately Printed, 1936. Price, $1.00. (Can be obtained from the New York Academy of Medicine.)

NEW EDITIONS.

Animal Micrology. Practical Exercises in Zoölogical Micro-Technique. By MICHAEL F. GUYER, Professor of Zoölogy in the University of Wisconsin. With a Chapter on Drawing by ELIZABETH A. (SMITH) BEAN, former Assistant Professor in Zoölogy in the University of Wisconsin. Pp. 331; 76 illustrations. Fourth edition, revised. Chicago: The University of Chicago Press, 1936. Price, $2.50.

Lehrbuch der Inneren Medizin. Vols. 1 and 2. By H. ASSMANN, G. v. BERGMANN <mit F. STROEBE>, H. BOHNENKAMP, R. DOERR, H. EPPINGER, E. GRAFE, FR. HELLER, G. KATSCH, P. MORAWITZ, A. SCHITTENHELM, R. SIEBECK, R. STAEHELIN, W. STEPP, H. STRAUB. Pp. Vol. 1, 934; Vol. 2, 846; illustrations, Vol. 1, 171; Vol. 2, 153. Dritte Umgearbeitete und Ergänzte Auflage. Berlin: Julius Springer, 1936. Price, Paper, RM 48; Bound, RM 52.

Post Mortems and Morbid Anatomy. By THEODORE SHENNAN, M.D., F.R.C.S. (EDIN.), Professor of Pathology in the University of Aberdeen. Pp. 716; 241 illustrations. Third edition. Baltimore: William Wood & Co., 1935. Price, $9.00. (Review, p. 279.)

The Extra-Ocular Muscles. A Clinical Study of Normal and Abnormal Ocular Motility. By LUTHER C. PETER, A.M., M.D., Sc.D., Professor of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania and the Rush Hospital for Consumption and Allied Diseases, etc. Pp. 351; 136 illustrations and 5 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, $4.50.

The second edition of this well-known book includes an entirely new chapter on operations on the ocular muscles, as practised by the author. Much new material has been added in the treatment of squint with fusion exercises.—F. A.

Urology in Women. A Handbook of Urinary Diseases in the Female Sex. By CATHERINE E. LEWIS, M.S. (LOND.), F.R.C.S. (ENG.), Surgeon to the Royal Free Hospital; Surgeon and Urologist to the South London Hospital for Women. Pp. 100; 31 illustrations, some in colors. Second edition. Baltimore: William Wood & Co., 1936. Price, $2.25.

Tumors of Bone (Including the Jaws and Joints). By CHARLES F. GESCHICKTER, M.D., and MURRAY M. COPELAND, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore. With Forewords by DEAN LEWIS, M.D., Professor of Surgery, Johns Hopkins Hospital and University, and the late JOSEPH COLT BLOODGOOD, M.D., former Clinical Professor of Surgery, Johns Hopkins Hospital and University, Baltimore. Pp. 832; 525 illustrations. Revised edition. New York: The American Journal of Cancer, 1936. Price, $6.00.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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BRONCHIECTASIS.

THE patient suffering from advanced bronchiectasis is a pathetic sight. He is usually an individual whose illness has lasted too long to permit his care at home by his family physician, in most cases he is not considered ill enough for hospital care, and hence he is most often seen in the outpatient department or he is permitted to care for himself as best he can without professional guidance. He is characterized by his sallow, pasty complexion and frequent cough, but more noticeably by the foul odor which has been compared, for want of more adequate description, to the odor of rotten eggs or limburger cheese. Even those who have the fortitude to attempt to carry on a gainful occupation, are prevented from earning a livelihood by the repellent odor. Normal social relations are denied him and he is compelled to live a secluded life.

This picture of the late stage of bronchiectasis does not represent the greater number of cases. However, the prognosis in the milder cases is grave since the disease as a rule becomes progressively worse.[1,2] Findley and Graham[3] state that in children, except for cases with slight dilatation of the bronchi, the condition increases in severity.

Bronchiectasis is said to be next to tuberculosis the most common of all chronic lung conditions. In fact Ochsner[4] places it above tuberculosis in regard to frequency of occurrence. Hamilton[5] states that of all inmates of tuberculosis sanitoria 25 to 50% are not tuberculous, a figure which seems unusually high.

The actual incidence is difficult to determine, since many of the milder forms are considered to be cases of chronic bronchitis. Others are considered to be cases of tuberculosis and are treated as such. One of our recent cases had been cared for in and out of a tuberculosis sanitarium as a case of pulmonary tuberculosis for 9 years. It is possible

that this man had pulmonary tuberculosis at one time but we were able to find no evidence of an active lesion at the time of our study.

Graham, Singer and Ballon[6,7] have pointed out the fact that many cases of bronchiectasis are considered tuberculosis but indicate that the error may also be made in diagnosing tuberculosis as bronchiectasis. Jex-Blake[8] states that of 29,700 patients admitted to the Bromptom Hospital for Consumptives 1.9% had a clinical diagnosis of bronchiectasis. He considered this figure as being too low and gave the probable figure as 5%. Since the publication of the paper by Jex-Blake the method of diagnosis has been improved by the introduction of iodized oil as a contrast medium,[9,10] and the incidence in a similar series would probably be higher. Lemon[11] reported an incidence of 0.4% from 15,500 admissions of children to the Mayo Clinic and Moll[12] also reported an incidence of 0.4% from 12,225 autopsy cases from the General Infirmary at Leeds. Ochsner[4] reported an incidence of 92% of definite bronchial dilatation in University students in whom a diagnosis of chronic bronchitis had been made. What portion of the student body this group comprised was not stated. The incidence of bronchiectasis in hospital populations or in postmortem series varies greatly.

An attempt to obtain statistical data from a large population has proven futile. In the Department of Commerce tables compiled from the United States registration area bronchiectasis is not mentioned as a cause of death. If we assume that chronic bronchitis severe enough to cause death, might be classed as bronchiectasis on the strength of Ochsner's[4] finding of an incidence of 92% for dilated bronchi in cases of chronic bronchitis, the death rate from this cause reaches 1.5 per 100,000.[13] These data are not too reliable, chiefly because of inadequacy of diagnosis. The figure is likely to be too low rather than too high, due to the tendency to diagnose chronic debilitating cough as tuberculosis. During the past few years many cases of bronchiectasis with mild symptoms associated with definitely dilated bronchi have been reported.[4,14,15]

Many theories have been advanced regarding the etiology of bronchiectasis, so many in fact that one is led at once to the conclusion that the cause of the condition cannot adequately be explained at this time by any one theory. It is apparent that the causes of bronchiectasis are numerous. One of the earliest theories of the etiology of bronchiectasis deals with changes in the wall of the bronchus and loss of contractility of the muscle.[16,17] Both of these early authors indicated their belief in the inception of bronchiectasis within the bronchus itself—a logical viewpoint which is still held by most observers. The actual process initiating the changes found in the bronchus is not always clear. There are some who maintain that disease of the bronchus is secondary to disease in the parenchyma of the lung causing fibrosis outside of the bronchus which, due to tension from without, causes dilatation of the bronchus.[18]

Various types of congenital abnormalities have been suggested as a cause of bronchiectasis. Chief among these abnormalities, especially in children, which have been suggested as important etiologic factors is congenital pulmonary atelectasis.[19,20,21]

Partial obstruction of the bronchi is associated frequently with bronchiectasis. Bronchiectasis is also found associated with foreign bodies and with bronchogenic carcinoma. Occasionally bronchiectasis is thought to result from tuberculosis as a sequel to associated bronchial obstruction and atelectasis. However, Boyd[1] could find no relationship between the two diseases in the cases which she studied.

That inflammatory changes are found within the bronchial wall in cases of bronchiectasis is so well known that the question as to whether the inflammation is the cause or result of dilatation of the bronchi is an important one. In the majority of instances the infection, if not the sole inciting cause, is at least an important factor in the damage to the wall of the bronchus and the progression of the condition. Except for the cases of congenital atelectasis, antecedent respiratory infection usually precedes the onset of bronchiectasis. Bronchopneumonia, influenza and pertussis are frequently found to have been inciting causes. Table 1 illustrates the relative frequency of the occurrence of respiratory diseases as etiologic factors in bronchiectasis.

TABLE 1.—INFECTIONS LEADING TO BRONCHIECTASIS.

Author.	Total No. of cases.	Pneumonia.	Pertussis.	Measles.	Influenza.	Bronchitis.	Upper respiratory infection.	Other causes.
Thorpe[22]	53	23	14	9	3	..	2	2
Lemon[11]	63	11	27	8	15	9	16	5
Boyd[1]	60	23	10	9	4	7	..	10
Moll[12]	65	27	6	..	1	14	..	17
Wall and Hoyle[15]	20	15	11	5	4			

In favor of the premise that the bronchiectasis is the result of infection is the work of Smith[23] and Pilot and Davis[24] who were able to recover spirochetes and fusiform bacilli from the majority of the cases of bronchiectasis studied. These organisms are commonly found in the mouth. In addition to finding spirochetes and fusiform bacilli, Smith was able to reproduce pulmonary lesions in the rabbit by intratracheal inoculation of fusospirochetal material.

The frequent finding of spirochetes and fusiform bacilli in cases of bronchiectasis does not constitute valid evidence that the organisms are responsible for the initiation of the disease. The experimental production of lung suppuration[25–28] indicates the possibility that certain cases are due primarily to the aspiration of material from the mouth into the lung and this offers one explanation for the production of lung abscess and bronchiectasis following tonsillectomy.

In a study of the bacteriology in cases of bronchiectasis Robinson and Greery,[29] and Boyd[1] report no predominating organisms. Ermatinger[30] likewise reported a wide variety of organisms from the sputum of bronchiectatic patients. Varney[31] reported the finding of the bacillus malenogenicum of Oliver and Wherry in 94% of unoperated cases of chronic lung abscess. He also found, by cultural means, *B. fusiformis* in all cases studied. Suffice it to say that a study of the sputum has not answered the question whether the organisms found were the causative agents or secondary invaders. It has been frequently suggested that

in addition to the infectious agents it is necessary to have other factors present, such as obstruction or trauma. In any case the mixed infection which is usually present is an important factor in the disease.[32] The relation of symbiosis of organisms in the production of necrotizing lesions has been well illustrated by Mason and Koch[33] to result from human bites.

The frequent occurrence of upper respiratory and sinus disease either antecedent to or associated with bronchiectasis has been referred to above. The thought that inflammation of the paranasal sinuses might contribute to the formation of ectatic bronchi has been frequently mentioned.[14,34–38]

Graham[35] has noted that during attacks of sinus disease in patients with bronchial fistulæ, the amount of discharge from the fistulæ increases. The increase of bronchorrhea during sinus attacks suggests that the entire respiratory tract is affected. The cause for this phenomenon is not apparent. That the excess secretion in the bronchi during paranasal sinus infections might be a factor in the production of bronchiectasis due to puddling is a possibility. Kern and Schenck[39] point out that chronic pulmonary infections likewise cause a reinfection of the nasal sinuses and thus a vicious cycle results.

In regard to our present knowledge of the etiology of bronchiectasis, contributing factors rather than a single cause should be considered. Graham, Singer and Ballon[6,7] state that "up to the present time it must be admitted that there is no prophylactic measure which carries with it the assurance that its employment will avoid the development of bronchiectasis." Nevertheless, careful study of each case should be made with respect to the factors involved, in the hope that these factors may be better understood and measures instituted for their correction early enough to prevent the inception of advanced bronchiectasis.

Within recent years several authors[40–43] have discussed the pathologic findings in bronchiectasis. The material for these studies was obtained from autopsy specimens and tissue removed at operation. As might be expected, the observations corroborate the description of such material to be found in earlier papers and textbooks of pathology. Erb's[40] observations were made upon material obtained from children whose symptoms had lasted from 2 weeks to $5\frac{1}{2}$ years. Realizing that the time element in the development of bronchiectatic lesions is not the only factor in the progression of the condition, he was able, however, to obtain specimens from patients in whom the duration of the disease was known and which showed varying stages of bronchiectasis. Erb was led to believe from his study that bronchiectasis is a progressive disease, and that two main stages may be recognized in the course of the disease: (1) the stage of damage or destruction and (2) the stage of repair. In those patients, the duration of whose disease was 6 weeks or less, there was no sign of regeneration of epithelium or of fibrosis. The specimens showed a purulent exudate within the bronchioles, ulceration of the mucous membrane, necrosis of a large part of the bronchial wall and the presence of exudate in the surrounding alveoli. In the early cases individual bronchi were dilated to varying degrees, the damage occurring somewhat irregularly within the bronchus. The first evidence

of repair was found by Erb[40] after 6 weeks following the onset of symptoms. This was evidenced by the appearance of epithelium approaching the squamous type instead of the normally occurring ciliated epithelium.

There appeared then a vascular granulation tissue lining the wall of the bronchus. The destroyed muscle and elastic tissue of the bronchus was wholly or in great part replaced by granulation tissue. Specimens from children whose disease was of several years' standing, showed marked fibrosis and thickening of the wall of the bronchi, with dilatation. The mucous membrane was thrown in folds and only occasionally ciliated epithelium was found. The parenchyma of the lung in the proximity of the bronchiectatic areas was fibrotic. Erb[40] believed that bronchiectasis has its origin in an acute respiratory inflammation and that obstruction favors the inflammatory process by prevention of drainage. Robinson,[41] studying specimens in much later stages than those described by Erb, noted that ciliated epithelium was consistently present, and the subepithelial tissue was of a granulomatous character. In addition to loss of muscle and elastic tissue the cartilaginous plates were in some instances replaced by fibrous tissue. Of importance is the fact that in 65% of the cases Robinson[41] found intimal thickening leading to stenosis of the bronchial arteries. The significance of these obliterating changes in the arteries is not known. While they are probably the result of inflammatory changes affecting all the tissues of the bronchus, it is likely that the reduced blood supply is associated with maintenance of the chronicity of the condition. This has been offered as one of the possible causes of bronchiectasis. To us, it appears more to be the result of the process than the cause.

Schneider[42] differentiates between atrophic and hypertrophic changes in the bronchi. In atrophic bronchiectasis he feels that the dilatations are likely to be cylindrical; in the hypertrophic, either cylindrical or saccular. In the hypertrophic form all layers of the bronchial wall are affected, while in the atrophic form, changes are found chiefly in the epithelial membrane. Since the atrophic form may change into the hypertrophic form this differentiation is not of great moment. Schneider believes, however, that the origin of these two forms is different, the atrophic form resulting from increased intrabronchial pressure; the hypertrophic resulting from infection of the bronchi subsequent in many instances to parenchymatous lung infection. This differentiation would not appear to be significant. Of more importance is the extent of the lesion and the amount of infection present. Ballon and Ballon,[44] and Bendove and Gershwin[45] have classified bronchial dilatations as regards form. Bendove and Gershwin have attempted to relate etiology, clinical picture and treatment to the type of bronchiectasis. These authors point out the need for further studies in the correlation of symptoms, signs and morphologic aspects of bronchiectasis. How far this relationship can be carried is difficult to state at this time. In many cases combinations of the usually recognized forms occur.

Much has been said regarding associated fibrotic changes in the parenchyma of the lung as a factor in the production of bronchiectasis. It has been frequently pointed out that fibrosis of the lung is not necessarily associated with bronchiectasis. The main pathologic findings in

bronchiectasis concern changes within the bronchi, not particularly related to parenchymal changes, so that it seems fair to conclude that associated parenchymal inflammation or fibrosis is the result and not the cause of bronchiectasis.

The clinical history and signs of bronchiectasis are quite variable. In the early stages or in the mild cases the physical findings may be quite insignificant. It is in this early period that it is important to detect the presence of changes in the bronchi. The usual diagnosis which is made in these cases is that of bronchitis and the usual symptom is a persistent cough. The cough is usually paroxysmal, more likely to occur at night when the patient lies down and may not be productive. If productive, the amount of mucoid sputum expectorated is as a rule small. Occasionally the sputum may be found to be blood-streaked. Seldom is the amount of blood brought up of a measurable quantity. In the mild cases fever is slight, if present. The patient may complain of feeling just a "bit below par," tiring easily and not feeling quite as energetic as usual. The onset of these symptoms is usually associated with an upper respiratory infection. The patient may have had an acute pulmonary infection or tracheobronchitis from which he did not seem entirely to recover. No less vague than the clinical history are the physical findings. In many of the early cases, even with the most careful examination, it may be impossible to detect any abnormal physical signs. The percussion note is usually normally resonant and equal on both sides of the chest. Fremitus, vocal or tactile, is not unusual. Expansion may be somewhat limited on the affected side. Unless a careful search is made, râles are often not heard, and if present are usually localized over small areas at the base. As a rule the râles are moist and apt to persist after coughing. Breath sounds and spoken and whispered voice sounds are generally transmitted well throughout the lung fields and may give no clue to the underlying lesion.

In later or more severe types of the disease the history and physical signs may be variable but more definitely indicate the existence of chronic pulmonary suppuration. Antecedent respiratory infection may or may not be noted by the patient as the origin of his illness. However, a history of frequent severe colds is not uncommon and many patients consider themselves so susceptible to common colds that they are led to believe that their illness is due to recurrent or persistent colds. Cough is frequent and expectoration may be copious. The amount of expectoration may vary from a few cubic centimeters to over a 1000 cc. a day. The expectorated material is watery and frothy and settles upon standing into definite layers. The odor of the sputum may not be unusual but as a rule the sputum has a rancid, or even fetid odor. In advanced cases fever is usually present, and occasionally the patient may have recurrent chills. Frequently the patient is able to correlate the bouts of chills and fever with a lessened amount of expectoration, but at times these occur even when drainage is copious.

In long standing cases there is clubbing of the fingers but the fact that a patient with bronchiectasis has clubbed fingers does not designate him as a case of long continued pulmonary disease since marked clubbing of the fingers may occur within a period of a few months.

Cyanosis and dyspnea may be present and may indicate an extensive lesion or the spread of infection to parenchymal tissue. Nausea and vomiting may occur from the odor of the sputum, from swallowing it, or may be an evidence of amyloid disease.

Physical findings vary from patient to patient, as well as in the same patient from time to time. The most consistent physical finding is the presence of moist, bubbling, râles at one or both bases, before, during and after coughing. In cases with associated pneumonitis or atelectasis or in which large sacculations are present, dullness may be elicited. Limitation of costal respiratory excursions is a common finding. The physical findings may be found to change in extent and degree following postural drainage. In regard to localization the condition is more frequently found in the left lower lobe, the right lower lobe being the next most frequently involved.

Dry bronchiectasis has been described by Bezançon and associates,[46] Scott Pinchin and Morlock,[47] Moll,[12] Wall and Hoyle[15] and others. It is a form in which gross infection is absent and the chief symptoms are cough and hemoptysis. Sputum may be entirely absent or expectorated in small amounts.

As has been so frequently pointed out by various authors, the only sure way to make the diagnosis of bronchiectasis is by Roentgen-ray with the aid of a contrast medium. This has been strikingly demonstrated by the fact that since Sicard and Forestier[9,10] introduced iodized oil as a means of contrast bronchography the number of cases correctly diagnosed has increased. Many cases considered as bronchiectasis have been found to be incorrectly diagnosed, and many patients have been found to have bronchiectasis in whom the condition was not suspected. Bronchography offers a criterion not only as to the presence or absence of bronchiectasis but as to the extent and distribution as well. It has been frequently pointed out that the ordinary chest plate without the use of contrast media is not sufficient evidence either for or against the presence of bronchiectasis.

Later stages of bronchiectasis may yield a roentgenogram which shows multiple fluid levels within the bronchi. At this stage the Roentgen-ray diagnosis is but confirmatory, as the diagnosis can be made easily from the clinical picture. In 1926 Graham and Singer[48] pointed out that dense triangular shadows in the region of the cardiodiaphragmatic area were present in bronchiectasis. The presence of triangular basal shadows was noted earlier by Armand-Delille, Levy and Marie.[49] Later Rist, Jacob and Trocme,[50] Sergent and Bordet[51] and Wallgren[52] were able to show by means of lipiodol injections that the triangular basal shadows contained bronchiectatic areas. Warner and Graham[53] state that "triangular shadows not only invariably indicated the presence of bronchiectasis, but they occurred frequently in the cases which we have studied." These authors state that these shadows were found in about 6% of all their proven cases of bronchiectasis. These authors also by a study of cases operated on and by animal experimentation proved that the shadows were due to atelectatic bronchiectatic lower lobes and further indicated that fibrosis of parenchyma of the lung or pleural involvement was not a necessarily associated condition. It

appears that the presence of a triangular basal shadow indicates the presence of bronchiectasis, but it must be kept in mind that the absence of these shadows does not indicate the absence of bronchiectasis. Contrast bronchography is a much more dependable criterion and while not infallible is the most accurate means of study.

During the past few years much has been written concerning the surgical treatment of bronchiectasis by lobectomy. The enthusiasm with which this form of treatment has been received, associated with the gravity of the prognosis in neglected cases, has fostered an undercurrent of opinion to the effect that other forms of treatment are of little value. Lobectomy for bronchiectasis, although suggested many years ago, was practically abandoned by 1922, undoubtedly due to the high mortality. Willy Meyer[54] reported a mortality of 50% in a collected series (16 cases). Graham[55], in 1923, reported 3 cases operated on, 2 of which died. He collected 45 additional cases from the literature, the mortality from the entire series being 52%. These figures, while indicating a mortality of consequence, hardly seem sufficient to account for the abandonment of the procedure since the cases chosen for operation were necessarily in a late stage of the disease and recovery by other means was not to be expected. Graham, Singer and Ballon[6,7] collected a series of 212 cases of bronchiectasis with an average mortality of approximately 34%. Coryllos[56] reported a series of 87 cases operated upon by 11 different surgeons with a mortality of 55.1%.

Janes [57] reported 17 cases from Shenstone's service. Of these, 3 cases died within a week following operation, while of 3 other cases which died, one survived 245 days. Of the 17 cases, 4 were reported cured, 5 improved, and 2 cases showed no improvement. Roberts and Nelson[58] reported 10 cases in which lobectomy was performed. Two of these were for carcinoma of the bronchus with bronchiectasis. Six patients were free from symptoms, and 2 patients succumbed as a result of the operation. Graham[6,7] has reported 6 additional cases of his own subjected to lobectomy, only 1 of which died. Other cases have been subjected to lobectomy within the past few years, many of which have not been reported.

The removal of one or more lobes of the lung for bronchiectasis has been performed sufficiently successfully by a number of surgeons and with mortalities low enough to stimulate continued use of the procedure. No doubt with additional experience the mortality will be still further reduced, as well as the postoperative morbidity.

The improvement in the mortality figures of cases recently operated on as compared to those previous to 1923 is in large part due to improvement in operative technique and anesthesia. The one-stage procedure of Brunn[59] is favored by some surgeons, while others believe that a two-stage procedure has definite advantages. The impetus for renewed attempts to remove bronchiectatic lobes surgically has come mainly as a result of better localization and understanding of the process. Many of the cases operated on before the use of iodized oil as a contrast medium for outlining the diseased bronchi were not suitable for operation. With a wider use of the procedure has come a better understanding of the criteria for the selection of cases.

Cases with many lobes involved, especially those with bilateral involvement, are not so amenable to surgical therapy as are the unilobar cases. Patients with continued septic febrile reactions are best not operated upon, unless drainage can be effected sufficient to allow the acute process to subside.

It is too early to predict the end results in the majority of cases reported as cured. Some of the patients who have been thought cured of their disease will no doubt develop other dilated bronchi or early involvement in other lobes will progress. However, the improvement brought to many warrants the continued use of the procedure. To those brought from the chronic invalidism of putrid, bronchial suppuration to health and clean breath, the risk involved must seem insignificant.

In addition to excision of the diseased lobe, two other methods of surgical removal have met with some success. Cautery pneumectomy, while a more prolonged procedure, has a lower mortality and is applicable to many cases unsuitable for radical lobectomy. Graham,[60] in a series of 54 cases of chronic pulmonary suppuration, had a mortality of 11%, improvement being noted in 41 cases.

Whittemore[61] has advocated the exteriorization of the affected lobe with subsequent removal by slough caused by constriction of the pedicle. This procedure with the attendant risk of secondary hemorrhage has not been widely adopted.

Drainage of bronchiectatic cavities through the chest wall has been associated with a high mortality, 62% Mumford, and Robinson,[62] and 73.3%, Körte,[63] and, unless followed by cautery pneumectomy, offers little in the way of curing the lesion.

Despite the many remarkable results attained, it must not be forgotten that methods of treatment other than surgical excision of diseased lobes are available. These methods are not only efficacious in selected cases as forms of palliative therapy but are useful and usually necessary in preparing the patient for lobectomy. Chief among the non-operative methods of treatment is drainage of the dilated cavities. The simplest method of affording drainage to bronchiectatic cavities is by means of coughing and posture. Stimulation rather than suppression of cough is indicated.[64] Frequently it is possible for the bronchiectatic patient to remain free of foul-smelling sputum, and in a fair state of health by routinely placing himself in a position favorable for emptying the dilated bronchi by means of gravity. Bronchoscopy in addition to its aid in diagnosis can materially aid in removing excessive amounts of puddled material from the bronchi.[65,66] The relation of accessory nasal sinus disease to bronchiectasis has been referred to. The importance of treating sinus infections in cases of bronchiectasis is now well known by all those interested in pulmonary suppuration.

The use of arsenicals directed against fusospirochetal infection so frequent in putrid bronchiectasis has no merit in affecting the dilatation of the bronchi. In the control of the superimposed infection it may be of some value.

Methods of treatment designed to empty bronchi by collapsing the lung have a very limited field of usefulness. When one examines the dilated bronchi in well developed cases of bronchiectasis, it is apparent

that collapse therapy can have little effect on the resistant, thickened, dilated bronchial walls. Graham,[60] however, reported a mild case in which this treatment was efficacious.

Phrenicectomy, artificial pneumothorax and thoracoplastic operations designed to obliterate dilated bronchi have been reported as successful in the treatment of bronchiectasis. The permanently improved cases are, however, few in number. In general these procedures alone have little value in the treatment of bronchiectasis. That these procedures may actually be detrimental has been suggested by some authors.[67] Graham, Singer and Ballon[6,7] offer the suggestion that phrenicectomy may be harmful in that it decreases the efficacy of natural mechanisms for emptying the bronchi. Associated with lobectomy these procedures have found favor either preliminary to or subsequent to the removal of the diseased lobe. At best medical treatment must be considered as palliative and not curative in well developed cases. Roles and Todd[67] reported that 10 of 14 cases of dry bronchiectasis treated medically became infected within 6 years. Of 49 cases of bronchiectasis treated medically, 23 were dead within a 6-year period and 9 were totally incapacitated. These authors feel that the results are poor not only because it fails to afford permanent relief, but because spread of the condition may and does occur in a short time and prevents patients from being suitable for radical therapy. They feel that lobectomy is the treatment of choice in all cases and warn against other forms of treatment. That these authors' pessimism concerning the efficacy of medical treatment is not wholly concurred in by their colleagues is evidenced by objections raised by letters to the *British Medical Journal* following the publication of their article.[47,68,69,70]

The indications for the various forms of treatment at the present time are not clearly defined. Bronchiectasis has always been a difficult condition to treat and the results have been generally poor. The renewed interest in this condition during the past few years will result in a better understanding of the possibilities of various forms of treatment but not until enough time has elapsed for a study of the end results over a long period. At present there is much divergence of opinion with regard to the best procedure in early mild cases. In advanced cases with hard fixed bronchi, lobectomy offers the best means of cure. Whether any true case of bronchiectasis is every cured by medical means is doubtful. That many are carried along in relatively satisfactory health is apparent. Whether early, mild localized cases should be subjected to lobectomy at a time when the operation is most likely to be successful, is in most cases decided by the patient, most of whom are unwilling to undergo a surgical procedure of such gravity unless quite ill. Each case requires individualization. The factors by which one may decide between palliation and an attempt at radical cure are numerous. The recent impetus to the surgical approach to this condition should clarify these factors.

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OPHTHALMOLOGY

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NUTRITIONAL DISEASES AND THE EYE. THE RÔLE OF VITAMIN B.

In the February, 1934, number of this Journal, Benedict reviewed the subject of nutritional diseases and the eye with special reference to the effects of deprivation of vitamin A. Brief mention was made of the report by Day, Langston and O'Brien on the development of cataracts in experimental animals on a diet low in vitamin G (B_2). Further studies on the ocular lesions produced by experimental deprivation of vitamin G have been carried on by O'Brien, by Langston, Day and Cosgrove,[1] and by Yudkin and his associates.[2] Langston, Day and Cosgrove reported the findings in a series of young albino mice which were placed on a diet entirely adequate except for the total absence of vitamin G. Seventy-nine per cent of the animals showed keratitis after an average of 43 days of the diet, 96% developed cataracts after an average of 48 days, and 57% developed general ophthalmia after an average of 50 days of the diet. These cataracts were primarily of cortical type but went on to complete, mature opacity of the lens if the animal lived long enough. Yudkin noted lenticular changes in 6 of 8 young rats kept for 10 weeks on a diet free from vitamin G. The lens changes developed completely in 7 days. He stated, however, that lens changes had not developed in older animals that had been kept for 3 months on a diet deficient in vitamin G, and

he was not sure that these experiments could be interpreted as indicating a cause of cataract in the human. He brought out the fact that the incidence of cataract in human pellagra was not especially high. O'Brien[3] was able to arrest the progress of lenticular changes in experimental animals by adding vitamin G to the diet, and in one of Yudkin's[2] rats an early opacity of the lens absorbed after feeding with vitamin G. Cosgrove[5] studied a series of patients with senile cataracts from the standpoint of vitamin G deficiency. He found that the majority of them ate only small amounts of food rich in vitamin G and that persons of similar age on a balanced diet did not develop cataracts to maturity during a 6-year period of observation.

In a further study of experimental cataract, Yudkin and Arnold[4] were able to produce cortical cataract in young rats after 70 to 94 days on a diet containing 70% lactose. Nuclear cataracts developed in young rats after 11 to 14 days on a diet containing 50% galactose, after 10 to 14 days with 35% galactose, and after 14 to 20 days with 25% galactose. In older rats, cortical cataracts developed after 21 days on a diet containing 50% galactose. Yudkin suggests that these cataracts may be caused by the disturbance of calcium metabolism induced by lactose and galactose or by the direct action on the lens of increased percentages of those sugars in the aqueous. The theory of faulty calcium metabolism is supported by the known clinical association of cataract with endemic and postoperative tetany, with rickets, and with spontaneous hypoparathyroidism.

In this country, at least, the association of ocular lesions with the vitamin G deficiency of primary pellagra has not received particular attention. The occurrence of pellagra-like syndromes secondary to gastro-intestinal disturbances and chronic alcoholism has been rather generally recognized. In 1934, Levine[6] reported a case of bilateral acute optic neuritis in "alcoholic pellagra." The neuritis cleared up with return of the vision to normal after several months on a balanced diet with added amounts of vitamin B_2. Levine stated that Quagliano had observed pellagrins with hemeralopia; that Bietti had seen optic neuritis in many cases of pellagra; that Krylov, in Russia, among 36 cases of pellagra, saw cataract formation even in children, paleness of the nerve heads, sluggish pupils, narrow vessels, scotomas for red and green in advanced cases, diplopia, hemeralopia and hallucinations, and that Kandelaki observed diplopia, cataracts and hemeralopia. These findings might be considered to indicate general nutritional deficiency rather than specific effects of vitamin G deprivation. Bristow[7] stated that routine and special examinations of the pellagrins admitted to the South Carolina State Hospital for the Insane had failed to reveal any very characteristic ocular lesions. A number of years ago the author had the opportunity of seeing quite a few cases of pellagra of varying degrees of severity. The only striking ocular complication noted was ulceration of the cornea in some of the more advanced cases. The eyes showed, as a rule, little inflammatory reaction, the ulcers responded very poorly to treatment and progressed to complete sloughing of the cornea in several instances.

The occurrence of ocular lesions in association with deficiencies of vitamin B_1 seems to be more definitely established than in the case

of vitamin B_2. It is true that primary beriberi is probably rare in this country. In other countries, retrobulbar optic neuritis has been reported in beriberi by Fernando,[8] by Shimazono, and by Katajama.[9] Katajama was able to demonstrate degeneration in the medullary sheaths and axis-cylinders of the optic nerves in experimental deprivation of vitamin B_1. Moore[10] reported a high percentage of visual defects apparently on the basis of retrobulbar neuritis occurring in a group of native South African students who lived largely on a diet of cooked manioc or cassava which contains a high percentage of starch. He noted that in the early phases of the disease, vision could be restored to normal by proper additions to the diet. In the more advanced stages, the visual defects were permanent. Moore was uncertain whether the optic nerve lesion was due to a vitamin deficiency or to a direct toxic effect of the manioc. He considered the vitamin deficiency the more likely cause. In this connection the case reported by Kepler[11] is of considerable interest. He found bilateral optic neuritis with secondary optic atrophy associated with a beriberi-like syndrome in a colored woman who had lived for some time on a diet consisting mainly of raw laundry starch.

In this country, however, more importance attaches to the types of deficiency neuritis which occur in association with dietary deficiencies resulting from gastro-intestinal disturbances of varying sorts. Christopher, Paskind and Snorf[12] reported 2 cases in which multiple neuritis developed after operations on the biliary tract. They expressed the opinion that the neuritis was due to avitaminosis resulting from prolonged postoperative vomiting which had lasted for 41 days in the first case and 43 days in the second case. Wechsler[13] reported 8 cases of multiple neuritis which he thought were caused by avitaminosis resulting from prolonged vomiting, gastro-intestinal disturbance, or restriction in diet. Recently, Wagener and Weir reported 2 cases of rapid loss of vision associated with nystagmus, ocular muscle paralysis, and mental confusion which occurred as complications of prolonged postoperative vomiting. The loss of vision was due in the first case to optic neuritis and in the second case to retrobulbar neuritis. The symptoms in both patients improved rapidly after the cessation of the vomiting and the addition of intramuscular doses of liver extract to a balanced diet.

Jolliffe, Colbert and Joffe[14] have confirmed the belief of Strauss that the peripheral polyneuritis of the alcohol addict is attributable to the deficiency of vitamin B_1 and not to the toxic effect of alcohol. It seems probable from the observations of Shastid,[15] Keefer[16] and others that the deficiency of vitamin B_1 resulting from restricted diet may be at least partially responsible for the retrobulbar optic neuritis or toxic amblyopia usually ascribed to the overuse of alcohol and tobacco. Addition of vitamin A (Yudkin[2]) or vitamin B_1 (Shastid[15]) to the diet is said to hasten recovery in these cases as well as in cases of optic neuritis of indeterminate origin. It has been suggested also by Keefer[16] that the retrobulbar optic neuritis seen at times in nursing mothers and spoken of hitherto as "lactation optic neuritis" may really be due to avitaminosis.

Winans and Perry[17] expressed the opinion that the polyneuritis associated with pernicious vomiting of pregnancy is a deficiency disease. They found that the disease responded favorably to the intramuscular administration of liver extract and they considered the deficiency to be largely one of vitamin B_1. Optic neuritis occurs at times in pernicious vomiting of pregnancy, often in association with polyneuritis or neuronitis as reported by Berkwitz and Lufkin.[18] In these cases the optic neuritis is most probably also due to deprivation of vitamin B_1. It seems probable that the hemorrhages in the retina which are seen in some severe cases of pernicious vomiting of pregnancy as reported by Stander[19] are also manifestations of vitamin deficiency, whether of vitamin B_1 or vitamin C it is difficult to say. However, in a case recently reported by Wagener and Weir, the hemorrhages disappeared rapidly under intramuscular administration of liver extract.

While clinical reports of ocular lesions dependent on or associated with deficiencies of vitamin B_1 and B_2 are rather scattered as yet, in this country at least, it would seem that enough experimental and clinical data are accumulating to indicate that deficiencies of these vitamins may play a more important rôle than is generally appreciated in the causation of acute and chronic affections of the optic nerve and perhaps of the ocular muscles and of hemorrhagic lesions of the retina. The words of Winans and Perry[17] might well be applied to optic neuritis and retrobulbar optic neuritis: "The nutritional background of a considerable portion of the population is such as to provide for the development of deficiency polyneuritis under a variety of conditions. Marked changes in the diet may decrease the intake of the vitamin B complex below the necessary minimum. Alcoholism, intestinal operations, and prolonged gastro-intestinal upsets, including the vomiting of pregnancy, may all serve to develop this disease. In any continued illness associated with loss of appetite, the possibility of the development of polyneuritis must be borne in mind."

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ERRATUM.

In the page advertisement in the July issue of The National Drug Company of Philadelphia the word grand appeared instead of the word giant. The paragraph should have read: "We offer a special Rag Weed Antigen Outfit complete for diagnosis and treatment of Fall Hay Fever for $10. Contains two diagnostic tests for mixed grasses and giant and dwarf rag weeds; 1 ampul-vial each Series 'AA', 'A' and 'B' Rag Weed Antigen; 25 cc. ampul-vial Sterile Salt Solution for dilution of antigen if needed; 25 cc. ampul-vial Epinephrin 1-1000 to control local or systemic reactions."

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